

# Document made available under the Patent Cooperation Treaty (PCT)

International application number: PCT/US05/003312

International filing date: 31 January 2005 (31.01.2005)

Document type: Certified copy of priority document

Document details: Country/Office: US  
Number: 10/830,477  
Filing date: 22 April 2004 (22.04.2004)

Date of receipt at the International Bureau: 31 March 2005 (31.03.2005)

Remark: Priority document submitted or transmitted to the International Bureau in compliance with Rule 17.1(a) or (b)



World Intellectual Property Organization (WIPO) - Geneva, Switzerland  
Organisation Mondiale de la Propriété Intellectuelle (OMPI) - Genève, Suisse

1300272

# THE UNITED STATES OF AMERICA

TO ALL TO WHOM THESE PRESENTS SHALL COME:

UNITED STATES DEPARTMENT OF COMMERCE

United States Patent and Trademark Office

*March 23, 2005*

**THIS IS TO CERTIFY THAT ANNEXED HERETO IS A TRUE COPY FROM THE RECORDS OF THE UNITED STATES PATENT AND TRADEMARK OFFICE OF THOSE PAPERS OF THE BELOW IDENTIFIED PATENT APPLICATION THAT MET THE REQUIREMENTS TO BE GRANTED A FILING DATE.**

**APPLICATION NUMBER: 10/830,477**

**FILING DATE: April 22, 2004**

**RELATED PCT APPLICATION NUMBER: PCT/US05/03312**



Certified by

Under Secretary of Commerce  
for Intellectual Property  
and Director of the United States  
Patent and Trademark Office

# HAMILTON, BROOK, SMITH & REYNOLDS, P.C.

042204

<b>UTILITY PATENT APPLICATION TRANSMITTAL</b> <small>(Only for new nonprovisional applications under 37 C.F.R. 1.53(b))</small>	Attorney Docket No.	2345.2051-005
	First Named Inventor or Application Identifier	Anna Helgadottir
	Express Mail Label No.	EV 052030802 US

Title of Invention	SUSCEPTIBILITY GENE FOR MYOCARDIAL INFARCTION, STROKE, AND PAOD METHODS OF TREATMENT
-----------------------	---

<b>APPLICATION ELEMENTS</b> See MPEP chapter 600 concerning utility patent application contents.	ADDRESS TO: <b>Mail Stop Patent Application Commissioner for Patents P.O. Box 1450 Alexandria, VA 22313-1450</b>
---	--

1. <input type="checkbox"/> Fee Transmittal Form <i>(Submit an original, and a duplicate for fee processing)</i>  2. <input checked="" type="checkbox"/> Specification <b>Total Pages [215]</b> <i>(preferred arrangement set forth below)</i> - Descriptive title of the invention - Cross References to Related Applications - Statement Regarding Fed sponsored R & D - Reference to sequence listing, a table, or a computer program listing appendix - Background of the Invention - Brief Summary of the Invention - Brief Description of the Drawings <i>(if filed)</i> - Detailed Description - Claim(s) - Abstract of the Disclosure  3. <input checked="" type="checkbox"/> Drawing(s) (35 U.S.C. 113) <b>Total Sheets [131]</b> <input type="checkbox"/> Fig. of the Drawings for Publication <input type="checkbox"/> <input checked="" type="checkbox"/> No Figure to be Published  4. <input type="checkbox"/> Oath or Declaration <b>Total Pages [ ]</b> a. <input type="checkbox"/> Newly executed (original or copy) b. <input type="checkbox"/> Copy from a prior application (37 C.F.R. 1.63(d)) <i>(for continuation/divisional with Box 17 completed)</i> i. <input type="checkbox"/> <b>DELETION OF INVENTOR(S)</b> Signed statement attached deleting inventor(s) named in the prior application, see 37 C.F.R. 1.63(d)(2) and 1.33(b).  5. <input type="checkbox"/> CD-ROM or CD-R in duplicate, large table or Computer Program <i>(Appendix)</i>	6. <input type="checkbox"/> Nucleotide and/or Amino Acid Sequence Submission <i>(if applicable, all necessary)</i> a. <input type="checkbox"/> Computer Readable Form b. <input type="checkbox"/> Paper Copy (identical to computer copy) [ ] Pages c. <input type="checkbox"/> Statements verifying identity of above copies  <table border="1" style="width: 100%; border-collapse: collapse;"> <tr> <th style="text-align: center;">ACCOMPANYING APPLICATION PARTS</th> </tr> <tr> <td>           7. <input type="checkbox"/> Assignment Papers (cover sheet &amp; documents)  <input checked="" type="checkbox"/> Assignee - deCODE genetics ehf. Reykjavik, ICELAND             8. <input type="checkbox"/> Power of Attorney <input type="checkbox"/> 37 C.F.R. 3.73(b) Statement            9. <input type="checkbox"/> English Translation Document <i>(if applicable)</i>            10. <input type="checkbox"/> Information Disclosure Statement (IDS)/PTO-1449 <input type="checkbox"/> Copies of IDS Citations            11. <input type="checkbox"/> Preliminary Amendment            12. <input checked="" type="checkbox"/> Return Receipt Postcard            13. <input type="checkbox"/> Small Entity Statement(s)            14a. <input type="checkbox"/> Foreign Priority Claim under 35 U.S.C. §119 or 365            14b. <input type="checkbox"/> Certified Copy of Priority Document(s)            15. <input type="checkbox"/> Nonpublication Request <i>(check parent application)</i>            16. <input type="checkbox"/> Other _____         </td> </tr> </table>	ACCOMPANYING APPLICATION PARTS	7. <input type="checkbox"/> Assignment Papers (cover sheet & documents) <input checked="" type="checkbox"/> Assignee - deCODE genetics ehf. Reykjavik, ICELAND  8. <input type="checkbox"/> Power of Attorney <input type="checkbox"/> 37 C.F.R. 3.73(b) Statement 9. <input type="checkbox"/> English Translation Document <i>(if applicable)</i> 10. <input type="checkbox"/> Information Disclosure Statement (IDS)/PTO-1449 <input type="checkbox"/> Copies of IDS Citations 11. <input type="checkbox"/> Preliminary Amendment 12. <input checked="" type="checkbox"/> Return Receipt Postcard 13. <input type="checkbox"/> Small Entity Statement(s) 14a. <input type="checkbox"/> Foreign Priority Claim under 35 U.S.C. §119 or 365 14b. <input type="checkbox"/> Certified Copy of Priority Document(s) 15. <input type="checkbox"/> Nonpublication Request <i>(check parent application)</i> 16. <input type="checkbox"/> Other _____
ACCOMPANYING APPLICATION PARTS			
7. <input type="checkbox"/> Assignment Papers (cover sheet & documents) <input checked="" type="checkbox"/> Assignee - deCODE genetics ehf. Reykjavik, ICELAND  8. <input type="checkbox"/> Power of Attorney <input type="checkbox"/> 37 C.F.R. 3.73(b) Statement 9. <input type="checkbox"/> English Translation Document <i>(if applicable)</i> 10. <input type="checkbox"/> Information Disclosure Statement (IDS)/PTO-1449 <input type="checkbox"/> Copies of IDS Citations 11. <input type="checkbox"/> Preliminary Amendment 12. <input checked="" type="checkbox"/> Return Receipt Postcard 13. <input type="checkbox"/> Small Entity Statement(s) 14a. <input type="checkbox"/> Foreign Priority Claim under 35 U.S.C. §119 or 365 14b. <input type="checkbox"/> Certified Copy of Priority Document(s) 15. <input type="checkbox"/> Nonpublication Request <i>(check parent application)</i> 16. <input type="checkbox"/> Other _____			

17. If a <b>CONTINUING APPLICATION</b> , check appropriate box; supply the requisite information.  <input type="checkbox"/> Continuation <input type="checkbox"/> Divisional <input checked="" type="checkbox"/> Continuation-in-part (CIP)    of prior application No.: 10/769,744 Prior application information:    Examiner:    Group Art Unit:	
The entire disclosure of the prior application is considered a part of the disclosure of the accompanying application and is hereby incorporated by reference. <i>(Add standard Related Applications section with incorporation by reference to specification or update same)</i>	

18. CORRESPONDENCE ADDRESS					
NAME	Customer No. 021005 HAMILTON, BROOK, SMITH & REYNOLDS, P.C.				
ADDRESS	530 Virginia Road, P.O. Box 9133				
CITY	Concord	STATE	MA	ZIP CODE	01742-9133
COUNTRY	USA	TELEPHONE	(978) 341-0036	FAX	(978) 341-0136

Signature		Date	April 22, 2004
Submitted by Typed or Printed Name	Elizabeth W. Mata	Reg. Number	38,236

-1-

Date: <u>4/22/04</u>	Express Mail Label No. <u>EV052030802 US</u>
----------------------	--

Inventors: Anna Helgadóttir, Mark Gurney, Jeffrey R. Gulcher and  
Hákon Hákonarson

Attorney's Docket No.: 2345.2051-005

SUSCEPTIBILITY GENE FOR MYOCARDIAL INFARCTION, STROKE,  
AND PAOD; METHODS OF TREATMENT

RELATED APPLICATIONS

This application is a continuation-in-part of U.S. Patent Application  
10/769,744, filed on January 30, 2004, which is a continuation-in-part of International  
5 Application No. PCT/US03/32556, which designated the United States and was filed  
on October 16, 2003, published in English, which claims the benefit of U.S.  
Provisional Application No. 60/419,433, filed on October 17, 2002 and U.S.  
Provisional Application No. 60/449,331, filed on February 21, 2003. The entire  
teachings of the above applications are incorporated herein by reference.

10

BACKGROUND OF THE INVENTION

Myocardial infarction (MI) and Acute Coronary Syndrome (ACS), *e.g.*, unstable  
angina, non-ST-elevation myocardial infarction (NSTEMI) or ST-elevation  
15 myocardial infarction (STEMI), are the leading causes of hospital admissions in  
industrialized countries. Cardiovascular disease continues to be the principle cause of  
death in the United States, Europe and Japan. The costs of the disease are high both  
in terms of morbidity and mortality, as well as in terms of the financial burden on  
health care systems.

20 Myocardial infarction generally occurs when there is an abrupt decrease in  
coronary blood flow following a thrombotic occlusion of a coronary artery previously  
damaged by atherosclerosis. In most cases, infarction occurs when an atherosclerotic  
plaque fissures, ruptures or ulcerates and when conditions favor thrombogenesis. In



rare cases, infarction may be due to coronary artery occlusion caused by coronary emboli, congenital abnormalities, coronary spasm, and a wide variety of systemic, particularly inflammatory diseases. Medical risk factors for MI include cigarette smoking, diabetes, hypertension and serum total cholesterol levels > 200 mg/dL, elevated serum LDL cholesterol, and low serum HDL cholesterol. Event rates in individuals without a prior history of cardiovascular disease are about 1%. In individuals who have had a first MI or ACS, the risk of a repeat MI within the next year is 10-14%, despite maximal medical management including angioplasty and stent placement.

Atherosclerosis can affect vascular beds in many large and medium arteries. Myocardial infarction and unstable angina (acute coronary syndrome (ACS)) stem from coronary artery atherosclerosis, while ischemic stroke most frequently is a consequence of carotid or cerebral artery atherosclerosis. Limb ischemia caused by peripheral arterial occlusive disease (PAOD) may occur as a consequence of iliac, femoral and popliteal artery atherosclerosis. The atherosclerotic diseases remain common despite the wide-spread use of medications that inhibit thrombosis (aspirin) or treat medical risk factors such as elevated cholesterol levels in blood (statins), diabetes, or hypertension (diuretics and anti-hypertensives).

Atherosclerotic disease is initiated by the accumulation of lipids within the artery wall, and in particular, the accumulation of low-density lipoprotein (LDL) cholesterol. The trapped LDL becomes oxidized and internalized by macrophages. This causes the formation of atherosclerotic lesions containing accumulations of cholesterol-engorged macrophages, referred to as "foam cells". As disease progresses, smooth muscle cells proliferate and grow into the artery wall forming a "fibrous cap" of extracellular matrix enclosing a lipid-rich, necrotic core. Present in the arterial walls of most people throughout their lifetimes, fibrous atherosclerotic plaques are relatively stable. Such fibrous lesions cause extensive remodeling of the arterial wall, outwardly displacing the external, elastic membrane, without reduction in luminal diameter or serious impact on delivery of oxygen to the heart. Accordingly, patients can develop large, fibrous atherosclerotic lesions without luminal narrowing until late in the disease process. However, the coronary arterial

lumen can become gradually narrowed over time and in some cases compromise blood flow to the heart, especially under high demand states such as exercise. This can result in reversible ischemia causing chest pain relieved by rest called stable angina.

5           In contrast to the relative stability of fibrous atherosclerotic lesions, the culprit lesions associated with myocardial infarction and unstable angina (each of which are part of the acute coronary syndrome) are characterized by a thin fibrous cap, a large lipid core, and infiltration of inflammatory cells such as T-lymphocytes and monocyte/macrophages. Non-invasive imaging techniques have shown that most  
10   MI's occur at sites with low- or intermediate- grade stenoses, indicating that coronary artery occlusion is due most frequently to rupture of culprit lesions with consequent formation of a thrombus or blood clot and not solely due to luminal narrowing by stenosis. Plaque rupture may be due to erosion or uneven thinning of the fibrous cap, usually at the margins of the lesion where macrophages enter, accumulate, and  
15   become activated by a local inflammatory process. Thinning of the fibrous cap may result from degradation of the extracellular matrix by proteases released from activated macrophages. These changes producing plaque instability and risk of MI may be augmented by production of tissue-factor procoagulant and other factors increasing the likelihood of thrombosis.

20           In acute coronary syndrome, the culprit lesion showing rupture or erosion with local thrombosis typically is treated by angioplasty or by balloon dilation and placement of a stent to maintain luminal patency. Patients experiencing ACS are at high risk for a second coronary event due to the multi-vessel nature of coronary artery disease with event rates approaching 10-14% within 12 months after the first incident.

25           The emerging view of MI is as an inflammatory disease of the arterial vessel wall on preexisting chronic atherosclerotic lesions, sometimes triggering rupture of culprit lesions and leading to local thrombosis and subsequent myocardial infarction. The process that triggers and sustains arterial wall inflammation leading to plaque instability is unknown, however, it results in the release into the circulation of tumor  
30   necrosis factor alpha and interleukin-6. These and other cytokines or biological mediators released from the damaged vessel wall stimulate an inflammatory response

in the liver causing elevation in several non-specific general inflammatory markers including C-reactive protein. Although not specific to atherosclerosis, elevated C-reactive protein (CRP) and serum amyloid A appear to predict risk for MI, perhaps as surrogates for vessel wall inflammation.

5        Although classical risk factors such as smoking, hyperlipidemia, hypertension, and diabetes are associated with many cases of coronary heart disease (CHD) and MI, many patients do not have involvement of these risk factors. In fact, many patients who exhibit one or more of these risk factors do not develop MI. Family history has long been recognized as one of the major risk factors. Although some of the familial  
10        clustering of MI reflects the genetic contribution to the other conventional risk factors, a large number of studies have suggested that there are significant genetic susceptibility factors, beyond those of the known risk factors (Friedlander Y, *et al.*, *Br. Heart J.* 1985; 53:382-7, Shea S. *et al.*, *J. Am. Coll. Cardiol.* 1984; 4:793-801, and Hopkins P.N., *et al.*, *Am. J. Cardiol.* 1988; 62:703-7). Major genetic  
15        susceptibility factors have only been identified for the rare Mendelian forms of hyperlipidemia such as a familial hypercholesterolemia.

Genetic risk is conferred by subtle differences in genes among individuals in a population. Genes differ between individuals most frequently due to single nucleotide polymorphisms (SNP), although other variations are also important. SNP  
20        are located on average every 1000 base pairs in the human genome. Accordingly, a typical human gene containing 250,000 base pairs may contain 250 different SNP. Only a minor number of SNP are located in exons and alter the amino acid sequence of the protein encoded by the gene. Most SNP have no effect on gene function, while others may alter transcription, splicing, translation, or stability of the mRNA encoded  
25        by the gene. Additional genetic polymorphism in the human genome is caused by insertion, deletion, translocation, or inversion of either short or long stretches of DNA. Genetic polymorphisms conferring disease risk may therefore directly alter the amino acid sequence of proteins, may increase the amount of protein produced from the gene, or may decrease the amount of protein produced by the gene.

30        As genetic polymorphisms conferring risk of disease are uncovered, genetic testing for such risk factors is becoming important for clinical medicine. Examples

are apolipoprotein E testing to identify genetic carriers of the apoE4 polymorphism in dementia patients for the differential diagnosis of Alzheimer's disease, and of Factor V Leiden testing for predisposition to deep venous thrombosis. More importantly, in the treatment of cancer, diagnosis of genetic variants in tumor cells is used for the selection of the most appropriate treatment regime for the individual patient. In breast cancer, genetic variation in estrogen receptor expression or heregulin type 2 (Her2) receptor tyrosine kinase expression determine if anti-estrogenic drugs (tamoxifen) or anti-Her2 antibody (Herceptin) will be incorporated into the treatment plan. In chronic myeloid leukemia (CML) diagnosis of the Philadelphia chromosome genetic translocation fusing the genes encoding the Bcr and Abl receptor tyrosine kinases indicates that Gleevec (STI571), a specific inhibitor of the Bcr-Abl kinase should be used for treatment of the cancer. For CML patients with such a genetic alteration, inhibition of the Bcr-Abl kinase leads to rapid elimination of the tumor cells and remission from leukemia.

Many general inflammatory markers predict risk of coronary heart disease, although these markers are not specific to atherosclerosis. For example, Stein (Stein, S., *Am J Cardiol*, 87 (suppl):21A-26A (2001)) discusses the use of any one of the following serum inflammatory markers as surrogates for predicting risk of coronary heart disease including C-reactive protein (CRP), serum amyloid A, fibrinogen, interleukin-6, tissue necrosis factor-alpha, soluble vascular cell adhesion molecules (sVCAM), soluble intervascular adhesion molecules (sICAM), E-selectin, matrix metalloprotease type-1, matrix metalloprotease type-2, matrix metalloprotease type-3, and matrix metalloprotease type-9. Elevation in one more of these serum inflammatory markers is not specific to coronary heart disease but also occurs with age or in association with cerebrovascular disease, peripheral vascular disease, non-insulin dependent diabetes, osteoarthritis, bacterial infection, and sepsis.

Serum C-reactive protein (CRP) is viewed as a convenient and sensitive marker of systemic inflammation. Generally CRP is measured in serum samples using commercially available enzyme-linked immunosorbent assays (EIA). Consistent across multiple published studies is the finding of a correlation between increased risk for coronary artery disease with increased serum CRP. For example, in the Women's

Health Study, CRP was measured in 27,939 apparently healthy American women. The cut-off points for quintiles of serum CRP in women were: less than or equal to 0.49, more than 0.49 to 1.08, more than 1.08 to 2.09, more than 2.09 to 4.19, and more than 4.19 mg CRP per liter, see Ridker, P.M. *et al.*, *New England. J. Med.*, 347: 1557-1565 (2001). In comparison to the lowest quintile, and even when adjusting for age, every quintile more than 0.49 mg CRP per liter was associated with increased risk for coronary heart disease with the highest relative risk of 4.5 seen for those women in the highest quintile of serum CRP (more than 4.19 mg CRP per liter). A similar correlation between increased serum CRP and increased risk for coronary heart disease in women has been reported (Ridker, P.M *et al.*, *New Engl. J. Med.*, 342:836-843 (2000) and Bermudez, E.A. *et al.*, *Arterioscler. Thromb. Vasc. Biol.*, 22: 1668-1673 (2002)). Men also show a correlation between increased serum inflammatory markers such as CR and increased risk for coronary heart disease has been reported (Doggen, C.J.M. *et al.*, *J. Internal Med.*, 248:406-414 (2000) and Ridker, P.M. *et al.*, *New England. J. Med.*, 336: 973-979 (1997)). Quintiles for serum CRP as reported by Doggen *et al.*, were less than 0.65, more than 0.65 to 1.18, more than 1.18 to 2.07, more than 2.07 to 4.23, and more than 4.23 mg CRP per liter. Unlike women, elevated serum CRP correlates with increased relative risk for coronary heart disease only in the 4<sup>th</sup> and 5<sup>th</sup> quintiles of CRP (relative risk of 1.7x and 1.9x, respectively).

Serum CRP in women also has been measured in conjunction with lipid markers such as levels of serum low density lipoprotein-cholesterol (LDL-C). In the study by Ridker, P.M. *et al.* (2002), serum CRP and LDL-C are minimally correlated, screening for both serum markers provided better prognostic indication than either alone. Thus, women with serum CRP above median values (more than 1.52 mg CRP per liter) and also serum LDL-C above median values (more than 123.7 mg LDL-C per deciliter) were at highest risk for coronary heart disease.

Elevated CRP or other serum inflammatory markers is also prognostic for increased risk of a second myocardial infarct in patients with a previous myocardial infarct (Retterstol, L. *et al.*, *Atheroscler.*, 160: 433-440 (2002)).

Since CRP is produced in the liver, there is no *a priori* mechanistic explanation for why elevation in CRP and other serum inflammatory markers should be prognostic for coronary artery disease. As discussed by Doggen, C.J.M., *et al.*, one or more of the following factors were speculated to account for the correlation observed:

5 (1) intrinsic inflammation and tissue damage within arterial lesions, (2) prior infection by *Helicobacter pylori* or by *Chlamydia pneumoniae*, (3) release of peptide cytokines including interleukin-6, or (4) activation of the complement system.

The end products of the leukotriene pathway are potent inflammatory lipid mediators derived from arachidonic acid. They can potentially contribute to

10 development of atherosclerosis and destabilization of atherosclerotic plaques through lipid oxidation and/or proinflammatory effects. LTC<sub>4</sub>, LTD<sub>4</sub>, and LTE<sub>4</sub>, are known to induce vasoconstriction. Allen *et al.*, *Circulation*, 97:2406-2413 (1998) described a novel mechanism in which atherosclerosis is associated with the appearance of a leukotriene receptor(s) capable of inducing hyperactivity of human epicardial

15 coronary arteries in response to LTC<sub>4</sub> and LTD<sub>4</sub>. LTB<sub>4</sub>, on the other hand, is a strong proinflammatory agent. Increased production of these end products, of the leukotriene pathway, could therefore serve as a risk factor for MI and atherosclerosis, whereas both inflammation and vasoconstriction/vasospasm have a well established role in the pathogenesis of MI and atherosclerosis. It has also been shown that a

20 heterozygous deficiency of the 5-LO enzyme in a knockout mouse model decreases atherosclerotic lesion size in LDLR<sup>-/-</sup> mice by about 95%. (Mehrabian *et al.*, *Circulation Research*. 91:120 (2002)). However, such genetic evidence for leukotriene involvement in MI or atherosclerosis in humans has not been reported. Mehrabian *et al.* did report a very small genetic association study looking for

25 correlation between promoter polymorphisms of 5-LO and carotid intimal thickening in normal individuals. However, their data paradoxically suggest that a lower amount of leukotriene production correlates with carotid atherosclerosis.

#### SUMMARY OF THE INVENTION

30 As described herein, a gene on chromosome 13q12-13 has been identified as playing a major role in myocardial infarction (MI). This gene, herein after referred to

as the MI gene, comprises nucleic acid that encodes 5-lipoxygenase activating protein (ALOX5AP or FLAP,) herein after referred to as FLAP. The gene has also been shown to play a role in stroke and PAOD.

The invention pertains to methods of treatment (prophylactic and/or therapeutic) for certain diseases and conditions (*e.g.*, MI, ACS, atherosclerosis, stroke, PAOD) associated with FLAP or with other members of the leukotriene pathway (*e.g.*, biosynthetic enzymes or proteins such as FLAP, arachidonate 4-lipoxygenase (5-LO), leukotriene C4 synthase (LTC4S), leukotriene A4 hydrolase (LTA4H), leukotriene B4 12-hydroxydehydrogenase (LTB4DH)); receptors and/or binding agents of the enzymes; and receptors for the leukotrienes LTA4, LTB4, LTC4, LTD4, LTE4, Cys LT1, Cys LT2, including leukotriene B4 receptor 1 (BLT1), leukotriene B4 receptor 2 (BLT2), cysteinyl leukotriene receptor 1 (CysLTR1), cysteinyl leukotriene receptor 2 (CysLTR2). The methods include the following: methods of treatment for myocardial infarction or susceptibility to myocardial infarction; methods of treatment for transient ischemic attack, transient monocular blindness or stroke, or susceptibility to stroke; methods of treatment for claudication, PAOD or susceptibility to PAOD; methods of treatment for acute coronary syndrome (*e.g.*, unstable angina, non-ST-elevation myocardial infarction (NSTEMI) or ST-elevation myocardial infarction (STEMI)); methods for reducing risk of MI, stroke or PAOD in persons with asymptomatic ankle/brachial index less than 0.9; methods for decreasing risk of a second myocardial infarction or stroke; methods of treatment for atherosclerosis, such as for patients requiring treatment (*e.g.*, angioplasty, stents, revascularization procedure) to restore blood flow in arteries (*e.g.*, coronary, carotid, and/or femoral arteries); methods of treatment for asymptomatic ankle/brachial index of less than 0.9; and/or methods for decreasing leukotriene synthesis (*e.g.*, for treatment of myocardial infarction, stroke or PAOD).

In the methods of the invention, a leukotriene synthesis inhibitor is administered to an individual in a therapeutically effective amount. The leukotriene synthesis inhibitor can be an agent that inhibits or antagonizes a member of the leukotriene synthesis pathway (*e.g.*, FLAP, 5-LO, LTC4S, LTA4H, and LTB4DH). For example, the leukotriene synthesis inhibitor can be an agent that inhibits or antagonizes FLAP

polypeptide activity (*e.g.*, a FLAP inhibitor) and/or FLAP nucleic acid expression, as described herein (*e.g.*, a FLAP nucleic acid antagonist). In another embodiment, the leukotriene synthesis inhibitor is an agent that inhibits or antagonizes polypeptide activity and/or nucleic acid expression of another member of the leukotriene biosynthetic pathway (*e.g.*, LTC4S, LTA4H) or that increases breakdown of leukotrienes (*e.g.*, LTB4DH). In preferred embodiments, the agent alters activity and/or nucleic acid expression of FLAP or of 5-LO. Preferred agents include those set forth in the Agent Table herein. In another embodiment, preferred agents can be: 1-((4-chlorophenyl)methyl)-3-((1,1-dimethylethyl)thio)-alpha,alpha-dimethyl-5-(2-quinolinylmethoxy)-1H-Indole-2-propanoic acid otherwise known as MK-0591, (R)-(+)-alpha-cyclopentyl-4-(2-quinolinylmethoxy)-Benzeneacetic acid otherwise known as BAY-x-1005, 3-(3-(1,1-dimethylethylthio-5-(quinoline-2-ylmethoxy))-1-(4-chloromethylphenyl)indole-2-yl)-2,2-dimethylpropionaldehyde oxime-0-2-acetic acid otherwise known as A-81834, optically pure enantiomers, salts, chemical derivatives, and analogues; or can be zileuton, atreleuton, 6-((3-fluoro-5-(tetrahydro-4-methoxy-2H-pyran-4yl)phenoxy)methyl)-1-methyl-2(1H)-quinolinone otherwise known as ZD-2138, 1-((4-chlorophenyl)methyl)-3-((1,1-dimethylethyl)thio)-alpha,alpha-dimethyl-5-(2-quinolinylmethoxy)-1H-Indole-2-propanoic acid otherwise known as MK-886, 4-(3-(4-(2-Methyl-imidazol-1-yl)-phenylsulfanyl)-phenyl)-tetrahydro-pyran-4-carboxylic acid amide otherwise known as CJ-13610, their optically pure enantiomers, salts, chemical derivatives, and analogues. In another embodiment, the agent alters metabolism or activity of a leukotriene (*e.g.*, LTA4, LTB4, LTC4, LTD4, LTE4, Cys LT1, Cys LT2), such as leukotriene antagonists or antibodies to leukotrienes, as well as agents which alter activity of a leukotriene receptor (*e.g.*, BLT1, BLT2, CysLTR1, and CysLTR2).

In certain embodiments of the invention, the individual is an individual who has at least one risk factor, such as an at-risk haplotype for myocardial infarction, stroke or PAOD; an at-risk haplotype in the FLAP gene; a polymorphism in a FLAP nucleic acid; an at-risk polymorphism in the 5-LO gene promoter, diabetes; hypertension; hypercholesterolemia; elevated triglycerides; elevated lp(a); obesity; ankle/brachial index (ABI) less than 0.9; a past or current smoker; transient ischemic attack;



transient monocular blindness; carotid endarterectomy; asymptomatic carotid stenosis; claudication; limb ischemia leading to gangrene, ulceration or amputation; a vascular or peripheral artery revascularization graft; an elevated inflammatory marker (*e.g.*, a marker such as C-reactive protein (CRP), serum amyloid A, fibrinogen, a leukotriene, 5 a leukotriene metabolite, interleukin-6, tissue necrosis factor-alpha, a soluble vascular cell adhesion molecule (sVCAM), a soluble intervascular adhesion molecule (sICAM), E-selectin, matrix metalloprotease type-1, matrix metalloprotease type-2, matrix metalloprotease type-3, matrix metalloprotease type-9, myeloperoxidase (MPO), and N-tyrosine); increased LDL cholesterol and/or decreased HDL 10 cholesterol; increased leukotriene synthesis; and/or at least one previous myocardial infarction, ACS, stable angina, previous transient ischemic attack, transient monocular blindness, or stroke, asymptomatic carotid stenosis or carotid endarterectomy, atherosclerosis, requires treatment for restoration of coronary artery blood flow (*e.g.*, angioplasty, stent, revascularization procedure).

15       The invention additionally pertains to methods of assessing an individual for an increased risk of MI, ACS, atherosclerosis, stroke, or PAOD, by assessing a level of a leukotriene metabolite (*e.g.*, LTE<sub>4</sub>, LTD<sub>4</sub>, LTB<sub>4</sub>) in the individual (*e.g.*, in a sample of blood, serum, plasma or urine). An increased level of leukotriene metabolite is indicative of an increased risk. The invention also encompasses methods of assessing 20 an individual for an increased risk of MI, ACS, atherosclerosis, stroke, transient ischemic attack, transient monocular blindness, asymptomatic carotid stenosis, PAOD, claudication, or limb ischemia, by stimulating production of a leukotriene or a leukotriene metabolite in a test sample from the individual (*e.g.*, a sample comprising neutrophils), using a calcium ionophore, and comparing the level of the leukotriene or 25 leukotriene metabolite with a control level. A level of production of the leukotriene or leukotriene metabolite that is significantly greater than the control level, is indicative of increased risk.

      The invention further pertains to methods of assessing response to treatment with a leukotriene synthesis inhibitor, by assessing a level of a leukotriene or 30 leukotriene metabolite in the individual before treatment, and comparing the level to a level of the leukotriene or leukotriene metabolite assessed during or after treatment.

A level that is significantly lower during or after treatment, than before treatment, is indicative of efficacy of the treatment with the leukotriene synthesis inhibitor. The invention additionally pertains to methods of assessing response to treatment with a leukotriene synthesis inhibitor, by stimulating production of a leukotriene or a  
5 leukotriene metabolite in a first test sample from the individual (e.g., a sample comprising neutrophils) before treatment, using a calcium ionophore, and comparing the level of the leukotriene or leukotriene metabolite with a level of production of the leukotriene or leukotriene in a second test sample from the individual, during or after treatment. A level of production of the leukotriene or leukotriene metabolite in the  
10 second test sample that is significantly lower than the level in the first test sample, is indicative of efficacy of the treatment. Similarly, the invention encompasses methods of assessing response to treatment with a leukotriene synthesis inhibitor, by assessing a level of an inflammatory marker in the individual before treatment, and during or after treatment. A level of the inflammatory marker during or after  
15 treatment, that is significantly lower than the level of inflammatory marker before treatment, is indicative of efficacy of the treatment.

The invention also pertains to use of leukotriene synthesis inhibitors for the manufacture of a medicament for the treatment of MI, ACS, stroke, PAOD, and/or atherosclerosis, as described herein, as well as for the manufacture of a medicament  
20 for the reduction of leukotriene synthesis.

#### BRIEF DESCRIPTION OF THE DRAWINGS

The foregoing and other objects, features and advantages of the invention will be apparent from the following more particular description of preferred embodiments  
25 of the invention.

FIG. 1 shows the results from a haplotype association case-control analysis of 437 female MI patients versus 721 controls using combinations 4 and 5 microsatellite markers to define the test haplotypes. The  $p$ -value of the association is plotted on the y-axis and position of markers on the x-axis. Only haplotypes that show association  
30 with a  $p$ -value  $< 10^{-5}$  are shown in the figure. The most significant microsatellite marker haplotype association is found using markers DG13S1103, DG13S166,

DG13S1287, DG13S1061 and DG13S301, with alleles 4, 0, 2, 14 and 3, respectively ( $p$ -value of  $1.02 \times 10^{-7}$ ). Carrier frequency of the haplotype is 7.3% in female MI patients and 0.3% in controls. The segment that is common to all the haplotypes shown in the figure includes only one gene, FLAP.

5           FIG. 2 shows the alleles of the markers defining the most significant microsatellite marker haplotypes. The segment defined with a black square is common to all the of most significantly associated haplotypes. The FLAP nucleic acid is located between makers DG13S166 and D13S1238. Two marker haplotype involving alleles 0 and -2 for markers DG13S166 and D13S1238, respectively, is  
10       found in excess in patients. Carrier frequency of this haploype is 27% in patients and 15.4% in controls ( $p$ -value  $1 \times 10^{-3}$ ). Therefore, association analysis confirms that the most tightly MI-associated gene within the linkage peak is FLAP.

          FIG. 3 shows the relative location of key SNPs and exons of the ALOX5AP/FLAP gene (exons shown in vertical rectangles). Haplotype length varies  
15       between 33 to 68 kb.

          FIG. 4 shows the amino acid sequence of FLAP (SEQ ID NO:2) and the mRNA of FLAP (SEQ ID NO: 3).

          FIG. 5 shows a significant positive correlation between serum LTE4 levels and serum CRP levels.

20           FIG. 6.1-6.82 show the genomic sequence of the FLAP gene (SEQ ID NO: 1).

          FIG. 7 depicts LTB4 production of ionomycin stimulated neutrophils from MI patients (n=41) and controls (n=35). The log-transformed (mean + SD) values measured at 15 and 30 minutes of stimulated cells are shown. (7.1) LTB4 production in MI patients and controls. The difference in the mean values between patients and  
25       the controls is tested using a two-sample t-test of the log-transformed values. (7.2) LTB4 production in MI male carriers and non-carriers of haplotype A4. Mean values of controls are included for comparison. Of note, males with the haplotype A4 produce the highest amounts of LTB4 ( $p < 0.005$  compared to controls). (7.3). Schematic representation of the 5-LO pathway with leukotriene bioactive products.

FIG. 8.1-8.40 show the sequences of the FLAP nucleic acid flanking the SNPs that were identified by sequencing samples from patients (SEQ ID NOs: 506-717).

FIG. 9 shows a schematic view of the chromosome 13 linkage region showing the FLAP gene. (9.1) The linkage scan for female MI patients and the one LOD drop region that includes the FLAP gene; (9.2) Microsatellite association for all MI patients: single marker association and two, three, four and five marker haplotype association. The arrows indicate the location of the most significant haplotype association across the FLAP gene in males and females. (9.3) The FLAP gene structure, with exons shown as cylinders, and the location of all the SNPs typed in the region (vertical lines). The vertical lines indicate the position of the microsatellites (shown in 9.2) and SNPs (shown in 9.3) used in the analysis.

FIG. 10 shows a linkage scan using framework microsatellite markers on chromosome 13 for male patients with ischemic stroke or TIA ( $n=342$  in 164 families at 6 meioses). The LOD score is expressed on the y axis and the distance from the pter in Kosambi cM on the x axis.

FIG. 11 shows a pairwise linkage disequilibrium (LD) between SNPs in a 60 kb region encompassing FLAP. The markers are plotted equidistantly. Two measures of LD are shown:  $D'$  in the upper left triangle and  $P$  values in the lower right triangle. Shaded lines indicate the positions of the exons of *FLAP* and the stars indicate the location of the markers of the at-risk haplotype A4. Scales for the LD strength are provided for both measures to the right.

#### DETAILED DESCRIPTION OF THE INVENTION

Extensive genealogical information has been combined with powerful gene sharing methods to map a gene on chromosome 13q12-13 that is associated with myocardial infarction. A genome wide search for susceptibility genes for MI, using a framework map of 1000 microsatellite markers, revealed a locus suggestive of linkage on 13q12-13. Sixty families with 159 female MI patients that clustered within and including 6 meiotic events were used in linkage analysis. At first, only female MI patients were used in the linkage analysis in an effort to enrich for patients with stronger genetic factors

contributing to their risk for MI. The epidemiological study of a population-based sample of Icelandic MI patients had previously suggested that the genetic factors for MI might be stronger for females than males, as the relative risk for siblings of female MI patients was significantly higher than the relative risk for siblings of male probands (1.59 (CI 1.47 - 1.73) vs. 1.35 (CI 1.28 - 1.42)) (unpublished data). The highest LOD score (2.5) was found at marker D13S289. The LOD score results for the families remained the same after adding 14 microsatellite markers to the candidate region. The inclusion of the additional markers increased the information on sharing by descent from 0.7 to 0.8, around the markers that gave the highest LOD scores. This linkage analysis mapped a gene contributing to MI to chromosome 13q12-13.

The candidate MI locus on chromosome 13q12-13 was then finely mapped with microsatellite markers. Patients with myocardial infarction and controls were initially genotyped with microsatellite markers with an average spacing between markers of less than 100 kb over the 12Mb candidate region. Initial haplotype association analysis that included all genotyped microsatellite markers across the MI candidate locus, resulted in several extended haplotypes composed of 4 and 5 microsatellite markers that were significantly associated with female MI (see, *e.g.*, Tables 14 and 15 below). A region common to all these extended haplotypes, is defined by markers DG13S166 and D13S1238. This region includes only one gene, the FLAP nucleic acid sequence. The two marker haplotype involving alleles 0 and -2 for markers DG13S166 and D13S1238, respectively, was found in excess in patients. Specific variants of the gene were then sought that were associated with MI.

In order to screen for SNPs in the FLAP gene, the whole gene was sequenced, both exons and introns. Initially, 9 SNPs identified within the gene were genotyped in patients and controls. Additional microsatellite markers close to or within the FLAP gene were also genotyped in all patients and controls. Five publicly known SNPs that are located within a 200 kb distance 5' to the FLAP gene were also genotyped in patients and controls. Haplotype association analysis in this case-control study including these additional markers showed several different variants of the same haplotype that were all significantly associated with female MI (see, *e.g.*, Table 8). Table 9 shows two haplotypes that are representative of these female MI risk haplotypes which are referred to herein as the female MI "at risk" haplotypes. The relative risk for male MI patients

that had the female MI-“at risk” haplotype was increased (see, *e.g.*, Table 9), indicating that the female MI-“at risk” haplotype also increased the risk of having an MI in males. These results further strengthened the hypothesis that the FLAP gene was an MI susceptibility gene.

5

*SNP haplotype association to MI, and subsequently to stroke and PAOD*

In an effort to identify haplotypes involving only SNP markers that associate with MI, additional SNPs were identified by sequencing the FLAP gene and the region flanking the gene. Currently, a total of 45 SNPs in 1343 patients and 624 unrelated  
10 controls have been genotyped. Two correlated series of SNP haplotypes have been observed in excess in patients, denoted as A and B in Table 7. The length of the haplotypes varies between 33 and 69 kb, and the haplotypes cover one or two blocks of linkage disequilibrium. Both series of haplotypes contain the common allele G of the SNP SG13S25. All haplotypes in the A series contain the SNP SG13S114, while all  
15 haplotypes in the B series contain the SNP SG13S106. In the B series, the haplotypes B4, B5, and B6 have a relative risk (RR) greater than 2 and with allelic frequencies above 10%. The haplotypes in the A series have slightly lower RR and lower p-values, but higher frequency (15-16%). The haplotypes in series B and A are strongly correlated, *i.e.*, the haplotypes in B define a subset of the haplotypes in A. Hence,  
20 haplotypes in series B are more specific than A. However, haplotypes in series A are more sensitive, *i.e.*, they capture more individuals with the putative mutation, as is observed in the population attributable risk which is less for B than for A. Furthermore, these haplotypes show similar risk ratios and allelic frequencies for early-onset patients (defined as onset of first MI before the age of 55) and for both genders. In addition,  
25 analyzing various groups of patients with known risk factors, such as hypertension, high cholesterol, smoking and diabetes, does not reveal any significant correlation with these haplotypes, suggesting that the haplotypes in the FLAP gene represent an independent genetic susceptibility factor for MI.

Because stroke and PAOD are diseases that are closely related to MI (all occur on  
30 the basis of atherosclerosis), the SNP haplotype in the FLAP gene that confers risk to MI was assessed to determine whether it also conferred risk of stroke and/or PAOD. Table 20 shows that haplotype A4 increases the risk of having a stroke to a similar extent as it

increases the risk of having an MI. Although not as significantly, haplotype A4 also confers risk of developing PAOD.

The FLAP nucleic acid encodes a 5-lipoxygenase activating protein, which, in combination with 5-lipoxygenase (5-LO), is required for leukotriene synthesis. FLAP  
5 acts coordinately with 5-LO to catalyze the first step in the synthesis of leukotrienes from arachidonic acid. It catalyzes the conversion of arachidonic acid to 5(S)-hydroperoxy-6-trans-8,11,14-cis-eicosatetraenoic acid (5-HPETE), and further to the allylic epoxide 5 (S)-trans7,9 trans 11,14-cis-eicosatetraenoic acid (leukotriene A4, LTA4).

The leukotrienes are a family of highly potent biological mediators of  
10 inflammatory processes produced primarily by bone marrow derived leukocytes such as monocytes, macrophages, and neutrophils. Both FLAP and 5-LO are detected within atherosclerosis lesions (Proc Natl Acad Sci U S A. 2003 Feb 4;100(3):1238-43.), indicating that the vessel itself can be a source of leukotrienes. It was found at first that the MI-risk FLAP haplotype was associated with higher serum leukotriene levels. Increased  
15 production of leukotriene in individuals with pre-existing atherosclerosis lesions may lead to plaque instability or friability of the fibrous cap leading to local thrombotic events. If this occurs in coronary artery arteries it leads to MI or unstable angina. If it occurs in the cerebrovasculature it leads to stroke or transient ischemic attack. If it occurs in large arteries to the limbs, it causes or exacerbates limb ischemia in persons  
20 with peripheral arterial occlusive disease (PAOD). Therefore, those with genetically influenced predisposition to produce higher leukotriene levels have higher risk for events due to pre-existing atherosclerosis such as MI.

Inhibitors of FLAP function impede translocation of 5-LO from the cytoplasm to the cell membrane and inhibit activation of 5-LO and thereby decrease leukotriene  
25 synthesis.

As a result of these discoveries, methods are now available for the treatment of myocardial infarction (MI) and acute coronary syndrome (ACS), as well as stroke and PAOD, through the use of leukotriene inhibitors, such as agents that inhibit leukotriene biosynthesis or antagonize signaling through leukotriene receptors. The term, "treatment"  
30 as used herein, refers not only to ameliorating symptoms associated with the disease or condition, but also preventing or delaying the onset of the disease or condition; preventing or delaying the occurrence of a second episode of the disease or condition;

and/or also lessening the severity or frequency of symptoms of the disease or condition. In the case of atherosclerosis, "treatment" also refers to a minimization or reversal of the development of plaques. Methods are additionally available for assessing an individual's risk for MI, ACS, stroke or PAOD. In a preferred embodiment, the individual to be  
5 treated is an individual who is susceptible (at increased risk) for MI, ACS, stroke or PAOD, such as an individual who is in one of the representative target populations described herein.

#### REPRESENTATIVE TARGET POPULATIONS

10 In one embodiment of the invention, an individual who is at risk for MI, ACS, stroke or PAOD is an individual who has an at-risk haplotype in FLAP, as described herein. In one embodiment, a haplotype associated with a susceptibility to myocardial infarction, ACS, stroke or PAOD comprises markers SG13S99, SG13S25, SG13S377, SG13S106, SG13S32 and SG13S35 at the 13q12-13 locus. In another embodiment, a  
15 haplotype associated with a susceptibility to myocardial infarction, ACS, stroke or PAOD comprises markers SG13S99, SG13S25, SG13S106, SG13S30 and SG13S42 at the 13q12 locus. In a third embodiment, a haplotype associated with a susceptibility to myocardial infarction, ACS, stroke or PAOD comprises markers SG13S25, SG13S106, SG13S30 and SG13S42 at the 13q12-13 locus. In a fourth embodiment, a haplotype  
20 associated with a susceptibility to myocardial infarction, ACS, stroke or PAOD comprises markers SG13S99, SG13S25, SG13S114, SG13S89 and SG13S32 at the 13q12-13 locus. In a fifth embodiment, a haplotype associated with a susceptibility to myocardial infarction, ACS, stroke or PAOD comprises markers SG13S25, SG13S114, SG13S89 and SG13S32 at the 13q12-13 locus. Additional haplotypes associated with a  
25 susceptibility to myocardial infarction, ACS, stroke or PAOD include the haplotypes shown in Tables 4, 8, 9, 14, 15, 17 and 19, as well as haplotypes comprising markers shown in Table 13.

Increased risk for MI, ACS, stroke or PAOD in individuals with a FLAP at-risk haplotype is logically conferred by increased production of leukotrienes in the arterial  
30 vessel wall or in bone-marrow derived inflammatory cells within the blood and/or arterial vessel wall. It is shown herein that FLAP at-risk haplotypes are associated with higher production of LTB<sub>4</sub> *ex vivo*. It is further shown herein that serum leukotriene



levels (specifically, leukotriene E4) correlate with serum CRP levels in myocardial infarction patients. FLAP genetic variation may drive high leukotriene levels (within the blood vessel and/or systemically), which in turn may drive higher CRP levels which has been shown as a risk factor for MI. Accordingly, individuals with a FLAP at-risk  
5 haplotype are likely to have elevated serum CRP as well as other serum inflammatory markers. The level of serum CRP or other serum inflammatory markers can be used as a surrogate for the level of arterial wall inflammation initiated by lipid deposition and atherogenesis conferred by the presence of the at-risk FLAP haplotype.

In another embodiment of the invention, an individual who is at risk for MI,  
10 ACS, stroke or PAOD is an individual who has a polymorphism in a FLAP gene, in which the presence of the polymorphism is indicative of a susceptibility to MI, ACS, stroke or PAOD. The term “gene,” as used herein, refers to not only the sequence of nucleic acids encoding a polypeptide, but also the promoter regions, transcription enhancement elements, splice donor/acceptor sites, and other non-transcribed nucleic  
15 acid elements. Representative polymorphisms include those presented in Table 13, below.

In a further embodiment of the invention, an individual who is at risk for MI, ACS, stroke or PAOD is an individual who has an at-risk polymorphism in the 5-LO gene in the promoter region, as described herein.

20 In a fourth embodiment, an individual who is at risk for MI, ACS, stroke or PAOD is an individual who has an elevated inflammatory marker. An “elevated inflammatory marker,” as used herein, is the presence of an amount of an inflammatory marker that is greater, by an amount that is statistically significant, than the amount that is typically found in control individual(s) or by comparison of disease risk in a  
25 population associated with the lowest band of measurement (*e.g.*, below the mean or median, the lowest quartile or the lowest quintile) compared to higher bands of measurement (*e.g.*, above the mean or median, the second, third or fourth quartile; the second, third, fourth or fifth quintile). An “inflammatory marker” refers to a molecule that is indicative of the presence of inflammation in an individual, for example, C-  
30 reactive protein (CRP), serum amyloid A, fibrinogen, leukotriene levels (*e.g.*, leukotriene B4, leukotriene C4), leukotriene metabolites (*e.g.*, leukotriene E4), interleukin-6, tissue necrosis factor-alpha, soluble vascular cell adhesion molecules (sVCAM), soluble

intervascular adhesion molecules (sICAM), E-selectin, matrix metalloprotease type-1, matrix metalloprotease type-2, matrix metalloprotease type-3, matrix metalloprotease type-9, myeloperoxidase (MPO), N-tyrosine) or other markers (see, *e.g.*, Doggen, C.J.M. *et al.*, *J. Internal Med.*, 248:406-414 (2000); Ridker, P.M. *et al.*, *New Englnd. J. Med.* 1997: 336: 973-979, Rettersol, L. *et al.*, 2002: 160:433-440; Ridker, P.M. *et. al.*, *New England. J. Med.*, 2002: 347: 1557-1565; Bermudez, E.A. *et .al.*, *Arterioscler. Thromb. Vasc. Biol.* , 2002: 22:1668-1673). In certain embodiments, the presence of such inflammatory markers can be measured in serum or urine.

In a fifth embodiment, an individual who is at risk for MI, ACS, stroke or PAOD is an individual who has increased LDL cholesterol and/or decreased HDL cholesterol levels. For example, the American Heart Association indicates that an LDL cholesterol level of less than 100 mg/dL is optimal; from 100-129 mg/dL is near/above optimal; from 130-159 mg/dL is borderline high; from 160-189 is high; and from 190 and up is very high. Therefore, an individual who is at risk for MI, ACS, stroke or PAOD because of an increased LDL cholesterol level is, for example, an individual who has more than 100 mg/dL cholesterol, such as an individual who has a near/above optimal level, a borderline high level, a high level or a very high level. Similarly, the American Heart Association indicates that an HDL cholesterol level of less than 40 mg/dL is a major risk factor for heart disease; and an HDL cholesterol level of 60 mg/dL or more is protective against heart disease. Thus, an individual who is at risk for MI, ACS, stroke or PAOD because of a decreased HDL cholesterol level is, for example, an individual who has less than 60 mg/dL HDL cholesterol, such as an individual who has less than 40 mg/dL HDL cholesterol.

In a sixth embodiment, an individual who is at risk for MI, ACS, stroke or PAOD is an individual who has increased leukotriene synthesis. "Increased leukotriene synthesis," as used herein, indicates an amount of production of leukotrienes that is greater, by an amount that is statistically significant, than the amount of production of leukotrienes that is typically found in control individual(s) or by comparison of leukotriene production in a population associated with the lowest band of measurement (*e.g.*, below the mean or median, the lowest quartile or the lowest quintile) compared to higher bands of measurement (*e.g.*, above the mean or median, the second, third or fourth quartile; the second, third, fourth or fifth quintile). For example, the FLAP at-risk

haplotypes correlate with increased serum leukotriene synthesis levels, and with increased production of leukotrienes *ex vivo*. An individual can be assessed for the presence of increased leukotriene synthesis by a variety of methods. For example, an individual can be assessed for an increased risk of MI, ACS, stroke, PAOD or  
5 atherosclerosis, by assessing the level of a leukotriene metabolite (*e.g.*, LTE<sub>4</sub>) in a sample (*e.g.*, serum, plasma or urine) from the individual. Samples containing blood, cells, or tissue can also be obtained from an individual and used to assess leukotriene or leukotriene metabolite production *ex vivo* under appropriate assay conditions. An increased level of leukotriene metabolites, and/or an increased level of leukotriene  
10 production *ex vivo*, is indicative of increased production of leukotrienes in the individual, and of an increased risk of MI, ACS, stroke, PAOD or atherosclerosis.

In a further embodiment, an individual who is at risk for MI, ACS, or stroke is an individual who has already experienced at least one MI, ACS event or stroke, or who has stable angina, and is therefore at risk for a second MI, ACS event or stroke. In another  
15 embodiment, an individual who is at risk for MI, ACS, stroke or PAOD is an individual who has atherosclerosis or who requires treatment (*e.g.*, angioplasty, stents, revascularization procedure) to restore blood flow in arteries.

In further embodiments, an individual who is at risk for MI, stroke or PAOD is an individual having asymptomatic ankle/brachial index of less than 0.9; an individual who  
20 is at risk for stroke, is an individual who has had one or more transient ischemic attacks; who has had transient monocular blindness; has had a carotid endarterectomy; or has asymptomatic carotid stenosis; an individual who is at risk for PAOD, is an individual who has (or had) claudication, limb ischemia leading to gangrene, ulceration or amputation, or has had a revascularization procedure.

25 In additional embodiments, an individual who is at risk for MI, ACS, stroke or PAOD is an individual who has diabetes; hypertension; hypercholesterolemia; elevated triglycerides (*e.g.*, > 200 mg/dl); elevated lp(a); obesity; ankle/brachial index (ABI) less than 0.9; and/or is a past or current smoker.

Individuals at risk for MI, ACS, stroke or PAOD may fall into more than one of  
30 these representative target populations. For example, an individual may have experienced at least one MI, ACS event, transient ischemic attack, transient monocular blindness, or stroke, and may also have an increased level of an inflammatory marker.

As used therein, the term “individual in a target population” refers to an individual who is at risk for MI, ACS, stroke or PAOD who falls into at least one of the representative target populations described above.

5           ASSESSMENT FOR AT-RISK HAPLOTYPES

A “haplotype,” as described herein, refers to a combination of genetic markers (“alleles”), such as those set forth in Table 13. In a certain embodiment, the haplotype can comprise one or more alleles (e.g., a haplotype containing a single SNP), two or more alleles, three or more alleles, four or more alleles, or five or more alleles. The  
10   genetic markers are particular “alleles” at “polymorphic sites” associated with FLAP. A nucleotide position at which more than one sequence is possible in a population (either a natural population or a synthetic population, *e.g.*, a library of synthetic molecules), is referred to herein as a “polymorphic site”. Where a polymorphic site is a single nucleotide in length, the site is referred to as a single nucleotide polymorphism (“SNP”).  
15   For example, if at a particular chromosomal location, one member of a population has an adenine and another member of the population has a thymine at the same position, then this position is a polymorphic site, and, more specifically, the polymorphic site is a SNP. Polymorphic sites can allow for differences in sequences based on substitutions, insertions or deletions. Each version of the sequence with respect to the polymorphic  
20   site is referred to herein as an “allele” of the polymorphic site. Thus, in the previous example, the SNP allows for both an adenine allele and a thymine allele.

Typically, a reference sequence is referred to for a particular sequence. Alleles that differ from the reference are referred to as “variant” alleles. For example, the reference FLAP sequence is described herein by SEQ ID NO: 1. The term, “variant FLAP”, as  
25   used herein, refers to a sequence that differs from SEQ ID NO: 1, but is otherwise substantially similar. The genetic markers that make up the haplotypes described herein are FLAP variants.

Additional variants can include changes that affect a polypeptide, *e.g.*, the FLAP polypeptide. These sequence differences, when compared to a reference nucleotide  
30   sequence, can include the insertion or deletion of a single nucleotide, or of more than one nucleotide, resulting in a frame shift; the change of at least one nucleotide, resulting in a change in the encoded amino acid; the change of at least one nucleotide, resulting in the

generation of a premature stop codon; the deletion of several nucleotides, resulting in a deletion of one or more amino acids encoded by the nucleotides; the insertion of one or several nucleotides, such as by unequal recombination or gene conversion, resulting in an interruption of the coding sequence of a reading frame; duplication of all or a part of a sequence; transposition; or a rearrangement of a nucleotide sequence, as described in detail above. Such sequence changes alter the polypeptide encoded by a FLAP nucleic acid. For example, if the change in the nucleic acid sequence causes a frame shift, the frame shift can result in a change in the encoded amino acids, and/or can result in the generation of a premature stop codon, causing generation of a truncated polypeptide.

Alternatively, a polymorphism associated with a susceptibility to MI, ACS, stroke or PAOD can be a synonymous change in one or more nucleotides (*i.e.*, a change that does not result in a change in the amino acid sequence). Such a polymorphism can, for example, alter splice sites, affect the stability or transport of mRNA, or otherwise affect the transcription or translation of the polypeptide. The polypeptide encoded by the reference nucleotide sequence is the “reference” polypeptide with a particular reference amino acid sequence, and polypeptides encoded by variant alleles are referred to as “variant” polypeptides with variant amino acid sequences.

Haplotypes are a combination of genetic markers, *e.g.*, particular alleles at polymorphic sites. The haplotypes described herein, *e.g.*, having markers such as those shown in Table 13, are found more frequently in individuals with MI, ACS, stroke or PAOD than in individuals without MI, ACS, stroke or PAOD. Therefore, these haplotypes have predictive value for detecting a susceptibility to MI, ACS, stroke or PAOD in an individual. The haplotypes described herein are in some cases a combination of various genetic markers, *e.g.*, SNPs and microsatellites. Therefore, detecting haplotypes can be accomplished by methods known in the art for detecting sequences at polymorphic sites, such as the methods described above.

In certain methods described herein, an individual who is at risk for MI, ACS, stroke or PAOD is an individual in whom an at-risk haplotype is identified. In one embodiment, the at-risk haplotype is one that confers a significant risk of MI, ACS, stroke or PAOD. In one embodiment, significance associated with a haplotype is measured by an odds ratio. In a further embodiment, the significance is measured by a percentage. In one embodiment, a significant risk is measured as an odds ratio of at

least about 1.2, including by not limited to: 1.2, 1.3, 1.4, 1.5, 1.6, 1.7, 1.8, and 1.9. In a further embodiment, an odds ratio of at least 1.2 is significant. In a further embodiment, an odds ratio of at least about 1.5 is significant. In a further embodiment, a significant increase in risk is at least about 1.7 is significant. In a further  
 5 embodiment, a significant increase in risk is at least about 20%, including but not limited to about 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, and 98%. In a further embodiment, a significant increase in risk is at least about 50%. In yet another embodiment, an at-risk haplotype has a p value  $< 0.05$ . It is understood however, that identifying whether a risk is medically significant may  
 10 also depend on a variety of factors, including the specific disease, the haplotype, and often, environmental factors.

An at-risk haplotype in, or comprising portions of, the FLAP gene, in one where the haplotype is more frequently present in an individual at risk for MI, ACS, stroke or PAOD (affected), compared to the frequency of its presence in a healthy individual  
 15 (control), and wherein the presence of the haplotype is indicative of susceptibility to MI, ACS, stroke or PAOD. As an example of a simple test for correlation would be a Fisher-exact test on a two by two table. Given a cohort of chromosomes the two by two table is constructed out of the number of chromosomes that include both of the haplotypes, one of the haplotype but not the other and neither of the haplotypes.

20 In certain embodiments, an at-risk haplotype is an at-risk haplotype within or near FLAP that significantly correlates with a haplotype such as a haplotype shown in Table 14; a haplotype shown in Table 15; a haplotype shown in Table 19; haplotype B4; haplotype B5; haplotype B6; haplotype A4; haplotype A5; or haplotype HapB. In other embodiments, an at-risk haplotype comprises an at-risk haplotype within or near  
 25 FLAP that significantly correlates with susceptibility to myocardial infarction or stroke. In a particular embodiment, a haplotype associated with a susceptibility to myocardial infarction, ACS, stroke or PAOD comprises markers SG13S99, SG13S25, SG13S377, SG13S106, SG13S32 and SG13S35 at the 13q12-13 locus. In another embodiment, a haplotype associated with a susceptibility to myocardial infarction, ACS, stroke or  
 30 PAOD comprises markers SG13S99, SG13S25, SG13S106, SG13S30 and SG13S42 at the 13q12-13 locus. In a third embodiment, a haplotype associated with a susceptibility to myocardial infarction, ACS, stroke or PAOD comprises markers SG13S25,

SG13S106, SG13S30 and SG13S42 at the 13q12-13 locus. In a fourth embodiment, a haplotype associated with a susceptibility to myocardial infarction, ACS, stroke or PAOD comprises markers SG13S99, SG13S25, SG13S114, SG13S89 and SG13S32 at the 13q12-13 locus. In other embodiments, the at-risk haplotype is selected from the

5 group consisting of: haplotype B4, B5, B6, A4 and A5. The at-risk haplotype can also comprise a combination of the markers in the haplotypes B4, B5, B6, A4 and/or A5. In further embodiments, the at-risk haplotype can be haplotype HapB. In other embodiments, the at-risk haplotype comprises a polymorphism shown in Table 13.

Standard techniques for genotyping for the presence of SNPs and/or microsatellite

10 markers can be used, such as fluorescent based techniques (Chen, *et al.*, *Genome Res.* 9, 492 (1999)), PCR, LCR, Nested PCR and other techniques for nucleic acid amplification. In a preferred embodiment, the method comprises assessing in an individual the presence or frequency of SNPs and/or microsatellites in, comprising portions of, the FLAP gene, wherein an excess or higher frequency of the SNPs and/or microsatellites compared to a

15 healthy control individual is indicative that the individual is susceptible to MI, ACS, stroke or PAOD. See, for example, Table 13 (below) for SNPs and markers that can form haplotypes that can be used as screening tools. These markers and SNPs can be identified in at-risk haplotypes. For example, an at-risk haplotype can include microsatellite markers and/or SNPs such as those set forth in Table 13. The presence of

20 the haplotype is indicative of a susceptibility to MI, ACS, stroke or PAOD, and therefore is indicative of an individual who falls within a target population for the treatment methods described herein.

Haplotype analysis involves defining a candidate susceptibility locus using LOD scores. The defined regions are then ultra-fine mapped with microsatellite markers with

25 an average spacing between markers of less than 100 kb. All usable microsatellite markers that are found in public databases and mapped within that region can be used. In addition, microsatellite markers identified within the deCODE genetics sequence assembly of the human genome can be used. The frequencies of haplotypes in the patient and the control groups can be estimated using an expectation-maximization

30 algorithm (Dempster A. *et al.*, 1977. *J. R. Stat. Soc. B*, 39:1-389). An implementation of this algorithm that can handle missing genotypes and uncertainty with the phase can be used. Under the null hypothesis, the patients and the controls are assumed to have

identical frequencies. Using a likelihood approach, an alternative hypothesis is tested, where a candidate at-risk-haplotype, which can include the markers described herein, is allowed to have a higher frequency in patients than controls, while the ratios of the frequencies of other haplotypes are assumed to be the same in both groups. Likelihoods  
5 are maximized separately under both hypotheses and a corresponding 1-df likelihood ratio statistic is used to evaluate the statistic significance.

To look for at-risk-haplotypes in the 1-lod drop, for example, association of all possible combinations of genotyped markers is studied, provided those markers span a practical region. The combined patient and control groups can be randomly divided  
10 into two sets, equal in size to the original group of patients and controls. The haplotype analysis is then repeated and the most significant p-value registered is determined. This randomization scheme can be repeated, for example, over 100 times to construct an empirical distribution of p-values. In a preferred embodiment, a p-value of  $<0.05$  is indicative of an at-risk haplotype.

15 A detailed discussion of haplotype analysis follows.

### *Haplotype analysis*

Our general approach to haplotype analysis involves using likelihood-based inference applied to NEsted MOdels. The method is implemented in our program  
20 NEMO, which allows for many polymorphic markers, SNPs and microsatellites. The method and software are specifically designed for case-control studies where the purpose is to identify haplotype groups that confer different risks. It is also a tool for studying LD structures.

When investigating haplotypes constructed from many markers, apart from  
25 looking at each haplotype individually, meaningful summaries often require putting haplotypes into groups. A particular partition of the haplotype space is a model that assumes haplotypes within a group have the same risk, while haplotypes in different groups can have different risks. Two models/partitions are nested when one, the alternative model, is a finer partition compared to the other, the null model, *i.e.*, the  
30 alternative model allows some haplotypes assumed to have the same risk in the null model to have different risks. The models are nested in the classical sense that the null model is a special case of the alternative model. Hence traditional generalized



likelihood ratio tests can be used to test the null model against the alternative model. Note that, with a multiplicative model, if haplotypes  $h_i$  and  $h_j$  are assumed to have the same risk, it corresponds to assuming that  $f_i/p_i = f_j/p_j$  where  $f$  and  $p$  denote haplotype frequencies in the affected population and the control population respectively.

5        One common way to handle uncertainty in phase and missing genotypes is a two-step method of first estimating haplotype counts and then treating the estimated counts as the exact counts, a method that can sometimes be problematic (*e.g.*, see the information measure section below) and may require randomization to properly evaluate statistical significance. In NEMO, maximum likelihood estimates, likelihood  
10 ratios and p-values are calculated directly, with the aid of the EM algorithm, for the observed data treating it as a missing-data problem.

NEMO allows complete flexibility for partitions. For example, the first haplotype problem described in the Methods section on Statistical analysis considers testing whether  $h_1$  has the same risk as the other haplotypes  $h_2, \dots, h_k$ . Here the  
15 alternative grouping is  $[h_1], [h_2, \dots, h_k]$  and the null grouping is  $[h_1, \dots, h_k]$ . The second haplotype problem in the same section involves three haplotypes  $h_1 = G0$ ,  $h_2 = GX$  and  $h_3 = AX$ , and the focus is on comparing  $h_1$  and  $h_2$ . The alternative grouping is  $[h_1], [h_2], [h_3]$  and the null grouping is  $[h_1, h_2], [h_3]$ . If composite alleles exist, one could collapse these alleles into one at the data processing stage, and performed the test as  
20 described. This is a perfectly valid approach, and indeed, whether we collapse or not makes no difference if there were no missing information regarding phase. But, with the actual data, if each of the alleles making up a composite correlates differently with the SNP alleles, this will provide some partial information on phase. Collapsing at the data processing stage will unnecessarily increase the amount of missing information. A  
25 nested-models/partition framework can be used in this scenario. Let  $h_2$  be split into  $h_{2a}, h_{2b}, \dots, h_{2e}$ , and  $h_3$  be split into  $h_{3a}, h_{3b}, \dots, h_{3e}$ . Then the alternative grouping is  $[h_1], [h_{2a}, h_{2b}, \dots, h_{2e}], [h_{3a}, h_{3b}, \dots, h_{3e}]$  and the null grouping is  $[h_1, h_{2a}, h_{2b}, \dots, h_{2e}], [h_{3a}, h_{3b}, \dots, h_{3e}]$ . The same method can be used to handle composite where collapsing at the data processing stage is not even an option since  $L_C$  represents multiple haplotypes  
30 constructed from multiple SNPs. Alternatively, a 3-way test with the alternative grouping of  $[h_1], [h_{2a}, h_{2b}, \dots, h_{2e}], [h_{3a}, h_{3b}, \dots, h_{3e}]$  versus the null grouping of  $[h_1,$

$h_{2a}, h_{2b}, \dots, h_{2e}, h_{3a}, h_{3b}, \dots, h_{3e}]$  could also be performed. Note that the generalized likelihood ratio test-statistic would have two degrees of freedom instead of one.

### *Measuring information*

5 Even though likelihood ratio tests based on likelihoods computed directly for the observed data, which have captured the information loss due to uncertainty in phase and missing genotypes, can be relied on to give valid p-values, it would still be of interest to know how much information had been lost due to the information being incomplete. Interestingly, one can measure information loss by considering a two-step  
10 procedure to evaluating statistical significance that appears natural but happens to be systematically anti-conservative. Suppose we calculate the maximum likelihood estimates for the population haplotype frequencies calculated under the alternative hypothesis that there are differences between the affected population and control population, and use these frequency estimates as estimates of the observed frequencies  
15 of haplotype counts in the affected sample and in the control sample. Suppose we then perform a likelihood ratio test treating these estimated haplotype counts as though they are the actual counts. We could also perform a Fisher's exact test, but we would then need to round off these estimated counts since they are in general non-integers. This test will in general be anti-conservative because treating the estimated counts as if they  
20 were exact counts ignores the uncertainty with the counts, overestimates the effective sample size and underestimates the sampling variation. It means that the chi-square likelihood-ratio test statistic calculated this way, denoted by  $\Lambda^*$ , will in general be bigger than  $\Lambda$ , the likelihood-ratio test-statistic calculated directly from the observed data as described in methods. But  $\Lambda^*$  is useful because the ratio  $\Lambda/\Lambda^*$  happens to be a  
25 good measure of information, or  $1 - (\Lambda/\Lambda^*)$  is a measure of the fraction of information lost due to missing information. This information measure for haplotype analysis is described in Nicolae and Kong, Technical Report 537, Department of Statistics, University of Statistics, University of Chicago, Revised for *Biometrics* (2003) as a natural extension of information measures defined for linkage analysis, and is  
30 implemented in NEMO.

### *Statistical analysis.*

For single marker association to the disease, the Fisher exact test can be used to calculate two-sided p-values for each individual allele. All p-values are presented unadjusted for multiple comparisons unless specifically indicated. The presented frequencies (for microsatellites, SNPs and haplotypes) are allelic frequencies as opposed to carrier frequencies. To minimize any bias due the relatedness of the patients who were recruited as families for the linkage analysis, first and second-degree relatives can be eliminated from the patient list. Furthermore, the test can be repeated for association correcting for any remaining relatedness among the patients, by extending a variance adjustment procedure (*e.g.*, as described in Risch, N. & Teng, J., "The relative power of family-based and case-control designs for linkage disequilibrium studies of complex human diseases I. DNA pooling," *Genome Res.* 8:1278-1288 (1998)) for sibships so that it can be applied to general familial relationships, and present both adjusted and unadjusted p-values for comparison. The differences are in general very small as expected. To assess the significance of single-marker association corrected for multiple testing we carried out a randomisation test using the same genotype data. Cohorts of patients and controls can be randomized and the association analysis redone multiple times (*e.g.*, up to 500,000 times) and the p-value is the fraction of replications that produced a p-value for some marker allele that is lower than or equal to the p-value we observed using the original patient and control cohorts.

For both single-marker and haplotype analyses, relative risk (RR) and the population attributable risk (PAR) can be calculated assuming a multiplicative model (haplotype relative risk model), (Terwilliger, J.D. & Ott, J., *Hum Hered*, 42, 337-46 (1992) and Falk, C.T. & Rubinstein, P, *Ann Hum Genet* 51 ( Pt 3), 227-33 (1987)), *i.e.*, that the risks of the two alleles/haplotypes a person carries multiply. For example, if RR is the risk of A relative to a, then the risk of a person homozygote AA will be RR times that of a heterozygote Aa and  $RR^2$  times that of a homozygote aa. The multiplicative model has a nice property that simplifies analysis and computations - haplotypes are independent, *i.e.*, in Hardy-Weinberg equilibrium, within the affected population as well as within the control population. As a consequence, haplotype counts of the affecteds and controls each have multinomial distributions, but with different haplotype frequencies under the alternative hypothesis. Specifically, for two

haplotypes  $h_i$  and  $h_j$ ,  $\text{risk}(h_i)/\text{risk}(h_j) = (f_i/p_i)/(f_j/p_j)$ , where  $f$  and  $p$  denote respectively frequencies in the affected population and in the control population. While there is some power loss if the true model is not multiplicative, the loss tends to be mild except for extreme cases. Most importantly, p-values are always valid since they are  
 5 computed with respect to null hypothesis.

In general, haplotype frequencies are estimated by maximum likelihood and tests of differences between cases and controls are performed using a generalized likelihood ratio test (Rice, J.A. *Mathematical Statistics and Data Analysis*, 602 (International Thomson Publishing, (1995)). deCODE's haplotype analysis program  
 10 called NEMO, which stands for NEsted MOdels, can be used to calculate all the haplotype results. To handle uncertainties with phase and missing genotypes, it is emphasized that we do not use a common two-step approach to association tests, where haplotype counts are first estimated, possibly with the use of the EM algorithm, Dempster, (A.P., Laird, N.M. & Rubin, D.B., *Journal of the Royal Statistical Society B*,  
 15 39, 1-38 (1971)) and then tests are performed treating the estimated counts as though they are true counts, a method that can sometimes be problematic and may require randomisation to properly evaluate statistical significance. Instead, with NEMO, maximum likelihood estimates, likelihood ratios and p-values are computed with the aid of the EM-algorithm directly for the observed data, and hence the loss of  
 20 information due to uncertainty with phase and missing genotypes is automatically captured by the likelihood ratios. Even so, it is of interest to know how much information is retained, or lost, due to incomplete information. Described herein is such a measure that is natural under the likelihood framework. For a fixed set of markers, the simplest tests performed compare one selected haplotype against all the  
 25 others. Call the selected haplotype  $h_1$  and the others  $h_2, \dots, h_k$ . Let  $p_1, \dots, p_k$  denote the population frequencies of the haplotypes in the controls, and  $f_1, \dots, f_k$  denote the population frequencies of the haplotypes in the affecteds. Under the null hypothesis,  $f_i = p_i$  for all  $i$ . The alternative model we use for the test assumes  $h_2, \dots, h_k$  to have the same risk while  $h_1$  is allowed to have a different risk. This implies that while  $p_1$  can be  
 30 different from  $f_1$ ,  $f_i/(f_2 + \dots + f_k) = p_i/(p_2 + \dots + p_k) = \beta_i$  for  $i = 2, \dots, k$ . Denoting  $f_i/p_1$  by  $r$ , and noting that  $\beta_2 + \dots + \beta_k = 1$ , the test statistic based on generalized likelihood ratios is

$$\Lambda = 2 \left[ \ell(\hat{r}, \hat{p}_1, \hat{\beta}_2, \dots, \hat{\beta}_{k-1}) - \ell(1, \tilde{p}_1, \tilde{\beta}_2, \dots, \tilde{\beta}_{k-1}) \right]$$

where  $\ell$  denotes log-likelihood and  $\tilde{\cdot}$  and  $\hat{\cdot}$  denote maximum likelihood estimates under the null hypothesis and alternative hypothesis respectively.  $\Lambda$  has asymptotically a chi-square distribution with 1-df, under the null hypothesis. Slightly more complicated null and alternative hypotheses can also be used. For example, let  $h_1$  be G0,  $h_2$  be GX and  $h_3$  be AX. When comparing G0 against GX, *i.e.*, this is the test which gives estimated RR of 1.46 and p-value = 0.0002, the null assumes G0 and GX have the same risk but AX is allowed to have a different risk. The alternative hypothesis allows, for example, three haplotype groups to have different risks. This implies that, under the null hypothesis, there is a constraint that  $f_1/p_1 = f_2/p_2$ , or  $w = [f_1/p_1]/[f_2/p_2] = 1$ . The test statistic based on generalized likelihood ratios is

$$\Lambda = 2 \left[ \ell(\hat{p}_1, \hat{f}_1, \hat{p}_2, \hat{w}) - \ell(\tilde{p}_1, \tilde{f}_1, \tilde{p}_2, 1) \right]$$

that again has asymptotically a chi-square distribution with 1-df under the null hypothesis. If there are composite haplotypes (for example,  $h_2$  and  $h_3$ ), that is handled in a natural manner under the nested models framework.

LD between pairs of SNPs can be calculated using the standard definition of  $D'$  and  $R^2$  (Lewontin, R., *Genetics* 49, 49-67 (1964) and Hill, W.G. & Robertson, A. *Theor. Appl. Genet.* 22, 226-231 (1968)). Using NEMO, frequencies of the two marker allele combinations are estimated by maximum likelihood and deviation from linkage equilibrium is evaluated by a likelihood ratio test. The definitions of  $D'$  and  $R^2$  are extended to include microsatellites by averaging over the values for all possible allele combination of the two markers weighted by the marginal allele probabilities. When plotting all marker combination to elucidate the LD structure in a particular region, we plot  $D'$  in the upper left corner and the p-value in the lower right corner. In the LD plots the markers can be plotted equidistant rather than according to their physical location, if desired.

### *Statistical Methods for Linkage Analysis*

Multipoint, affected-only allele-sharing methods can be used in the analyses to assess evidence for linkage. Results, both the LOD-score and the non-parametric linkage (NPL) score, can be obtained using the program Allegro (Gudbjartsson *et al.*, *Nat. Genet.* 25:12-3, 2000). Our baseline linkage analysis uses the Spairs scoring function (Whittemore, A.S., Halpern, J. (1994), *Biometrics* 50:118-27; Kruglyak L, *et*

*al.* (1996), *Am J Hum Genet* 58:1347-63), the exponential allele-sharing model (Kong, A. and Cox, N.J. (1997), *Am J Hum Genet* 61:1179-88) and a family weighting scheme that is halfway, on the log-scale, between weighting each affected pair equally and weighting each family equally. The information measure we use is part of the Allegro  
 5 program output and the information value equals zero if the marker genotypes are completely uninformative and equals one if the genotypes determine the exact amount of allele sharing by descent among the affected relatives (Gretarsdottir *et al.*, *Am. J. Hom. Genet*, 70:593-603, (2002)). We computed the P-values two different ways and here report the less significant result. The first P-value can be computed on the basis of  
 10 large sample theory; the distribution of  $Z_{lr} = \sqrt{2[\log_e(10)\text{LOD}]}$  approximates a standard normal variable under the null hypothesis of no linkage (Kong, A. and Cox, N.J. (1997), *Am J Hum Genet* 61:1179-88). The second P-value can be calculated by comparing the observed LOD-score with its complete data sampling distribution under the null hypothesis (e.g., Gudbjartsson *et al.*, *Nat. Genet.* 25:12-3, 2000). When the  
 15 data consist of more than a few families, these two P-values tend to be very similar.

#### METHODS OF TREATMENT

The present invention encompasses methods of treatment (prophylactic and/or therapeutic, as described above) for MI, ACS, stroke or PAOD in individuals, such as  
 20 individuals in the target populations described above, as well as for other diseases and conditions associated with FLAP or with other members of the leukotriene pathway (e.g., for atherosclerosis). Members of the "leukotriene pathway," as used herein, include polypeptides (e.g., enzymes, receptors) and other molecules that are associated with production of leukotrienes: for example, proteins or enzymes such as  
 25 FLAP, 5-LO, other leukotriene biosynthetic enzymes (e.g., leukotriene C4 synthase, leukotriene A4 hydrolase); receptors or binding agents of the enzymes; leukotrienes such as LTA4, LTB4, LTC4, LTD4, LTE4; and receptors of leukotrienes (e.g., leukotriene B4 receptor 1 (BLT1), leukotriene B4 receptor 2 (BLT2), cysteinyl leukotriene receptor 1 (CysLTR1), cysteinyl leukotriene receptor 2 (CysLTR2)).

30 In particular, the invention relates to methods of treatment for myocardial infarction or susceptibility to myocardial infarction (for example, for individuals in an at-risk population such as those described above); as well as methods of treatment for

acute coronary syndrome (*e.g.*, unstable angina, non-ST-elevation myocardial infarction (NSTEMI) or ST-elevation myocardial infarction (STEMI)); methods for reducing risk of MI, stroke or PAOD in persons with asymptomatic ankle/brachial index less than 0.9; for decreasing risk of a second myocardial infarction; for stroke  
5 or susceptibility to stroke; for transient ischemic attack; for transient monocular blindness; for decreasing risk of a second stroke; for PAOD or susceptibility to PAOD; for ABI less than 0.9; for claudication or limb ischemia; for atherosclerosis, such as for patients requiring treatment (*e.g.*, angioplasty, stents, revascularization procedure) to restore blood flow in arteries (*e.g.*, coronary, carotid, and/or femoral  
10 arteries); for treatment of asymptomatic ankle/brachial index of less than 0.9; and/or for decreasing leukotriene synthesis (*e.g.*, for treatment of MI, ACS, stroke or PAOD). The invention additionally pertains to use of one or more leukotriene synthesis inhibitors, as described herein, for the manufacture of a medicament for the treatment of MI, ACS, stroke, PAOD and/or atherosclerosis, *e.g.*, using the methods  
15 described herein.

In the methods of the invention, a “leukotriene synthesis inhibitor” is used. In one embodiment, a “leukotriene synthesis inhibitor” is an agent that inhibits FLAP polypeptide activity and/or FLAP nucleic acid expression, as described herein (*e.g.*, a nucleic acid antagonist). In another embodiment, a leukotriene synthesis inhibitor is  
20 an agent that inhibits polypeptide activity and/or nucleic acid expression of another member of the leukotriene biosynthetic pathway (*e.g.*, 5-LO; LTC4S; LTA4H; LTB4DH). In still another embodiment, a leukotriene synthesis inhibitor is an agent that alters activity or metabolism of a leukotriene (*e.g.*, an antagonist of a leukotriene; an antagonist of a leukotriene receptor). In preferred embodiments, the leukotriene  
25 synthesis inhibitor alters activity and/or nucleic acid expression of FLAP or of 5-LO, or alters interaction between FLAP and 5-LO.

Leukotriene synthesis inhibitors can alter polypeptide activity or nucleic acid expression of a member of the leukotriene pathway by a variety of means, such as, for example, by catalytically degrading, downregulating or interfering with the  
30 expression, transcription or translation of a nucleic acid encoding the member of the leukotriene pathway; by altering posttranslational processing of the polypeptide; by altering transcription of splicing variants; or by interfering with polypeptide activity

(e.g., by binding to the polypeptide, or by binding to another polypeptide that interacts with that member of the leukotriene pathway, such as a FLAP binding agent as described herein or some other binding agent of a member of the leukotriene pathway; by altering interaction among two or more members of the leukotriene pathway (e.g., interaction between FLAP and 5-LO); or by antagonizing activity of a member of the leukotriene pathway.

Representative leukotriene synthesis inhibitors include the following:

agents that inhibit activity of a member of the leukotriene biosynthetic pathway (e.g., FLAP, 5-LO), LTC4S, LTA4H, such as the agents presented in the Agent Table below; agents that inhibit activity of receptors of members of the leukotriene pathway, such as FLAP receptors, LTA4 receptors, LTB4 receptors, LTC4 receptors, LTD4 receptors, LTE4 receptors, Cys LT1 receptors, Cys LT2 receptors, 5-LO receptors; BLT1; BLT2; CysLTR1; CysLTR2; agents that bind to the members of the leukotriene pathway, such as FLAP binding agents (e.g., 5-LO) or agents that bind to receptors of members of the leukotriene pathway (e.g., leukotriene receptor antagonists); agents that bind to a leukotriene (e.g., to LTA4, LTB4, LTC4, LTD4, LTE4, Cys LT1, Cys LT2); agents that increase breakdown of leukotrienes (e.g., LTB4DH); or other agents that otherwise affect (e.g., increase or decrease) activity of the leukotriene;

antibodies to leukotrienes;

antisense nucleic acids or small double-stranded interfering RNA, to nucleic acids encoding FLAP, 5-LO, or a leukotriene synthetase or other member of the leukotriene pathway, or fragments or derivatives thereof, including antisense nucleic acids to nucleic acids encoding the FLAP, 5-LO or leukotriene synthetase polypeptides, and vectors comprising such antisense nucleic acids (e.g., nucleic acid, cDNA, and/or mRNA, double-stranded interfering RNA, or a nucleic acid encoding an active fragment or derivative thereof, or an oligonucleotide; for example, the complement of one of SEQ ID Nos. 1 or 3, or a nucleic acid complementary to the nucleic acid encoding SEQ ID NO: 2, or fragments or derivatives thereof);



peptidomimetics; fusion proteins or prodrugs thereof; ribozymes; other small molecules; and

5 other agents that alter (*e.g.*, inhibit or antagonize) expression of a member of the leukotriene pathway, such as FLAP or 5-LO nucleic acid expression or polypeptide activity, or that regulate transcription of FLAP splicing variants or 5-LO splicing variants (*e.g.*, agents that affect which splicing variants are expressed, or that affect the amount of each splicing variant that is expressed).

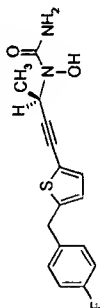
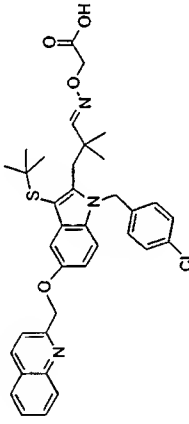
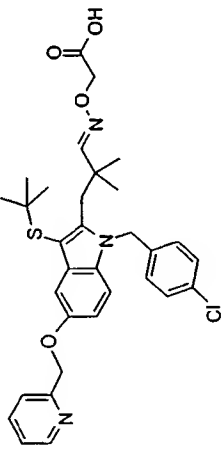
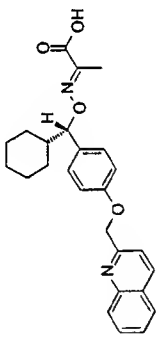
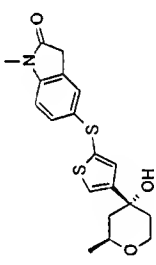
10 More than one leukotriene synthesis inhibitor can be used concurrently, if desired.

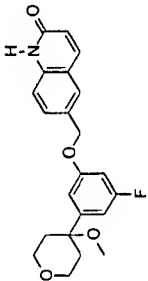
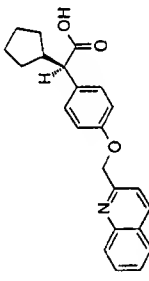
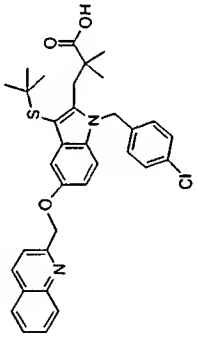
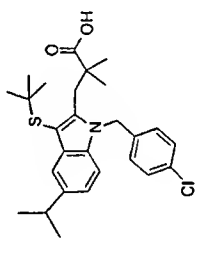
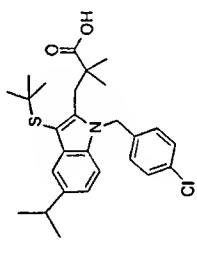

The therapy is designed to alter activity of a FLAP polypeptide, a 5-LO polypeptide, or another member of the leukotriene pathway in an individual, such as by inhibiting or antagonizing activity. For example, a leukotriene synthesis inhibitor  
15 can be administered in order to decrease synthesis of leukotrienes within the individual, or to downregulate or decrease the expression or availability of the FLAP nucleic acid or specific splicing variants of the FLAP nucleic acid. Downregulation or decreasing expression or availability of a native FLAP nucleic acid or of a particular splicing variant could minimize the expression or activity of a defective  
20 nucleic acid or the particular splicing variant and thereby minimize the impact of the defective nucleic acid or the particular splicing variant. Similarly, for example, a leukotriene synthesis inhibitor can be administered in order to downregulate or decrease the expression or availability of the nucleic acid encoding 5-LO or specific splicing variants of the nucleic acid encoding 5-LO.

25 The leukotriene synthesis inhibitor(s) are administered in a therapeutically effective amount (*i.e.*, an amount that is sufficient to treat the disease or condition, such as by ameliorating symptoms associated with the disease or condition, preventing or delaying the onset of the disease or condition, and/or also lessening the severity or frequency of symptoms of the disease or condition). The amount which  
30 will be therapeutically effective in the treatment of a particular individual's disease or condition will depend on the symptoms and severity of the disease, and can be determined by standard clinical techniques. In addition, *in vitro* or *in vivo* assays may optionally be employed to help identify optimal dosage ranges. The precise dose to

be employed in the formulation will also depend on the route of administration, and the seriousness of the disease or disorder, and should be decided according to the judgment of a practitioner and each patient's circumstances. Effective doses may be extrapolated from dose-response curves derived from *in vitro* or animal model test  
5 systems.

In preferred embodiments of the invention, the leukotriene synthesis inhibitor agent is an agent that inhibits activity of FLAP and/or of 5-LO. Preferred agents include the following, as set forth in the Agent Table:

Company	Product Name (Code)	Structure	Chemical Name	Patent Ref	Date Patent Issued/Applica tion Published	MOA
Abbott	aireleuton (ABT-761)		(R)-(+)-N-[3-[5-[(4-fluorophenyl)methyl]-2-thienyl]-1-methyl-2-propynyl]-N-hydroxurea	US 5288751, US 5288743, US 5616596	2/22/94 04/01/97	5-LPO inhibitor
Abbott	A-81834		3-(3-(1,1-dimethylethylthio-5-(quinoline-2-ylmethoxy)-1-(4-chloromethylphenyl)indole-2-yl)-2,2-dimethylpropionaldehyde oxime-0-2-acetic acid	WO9203132, US 5459150	3/5/1992, 10/17/95	FLAP inhibitor
Abbott	A-86886		3-(3-(1,1-dimethylethylthio-5-(pyridin-2-ylmethoxy)-1-(4-chloromethylphenyl)indole-2-yl)-2,2-dimethylpropionaldehyde oxime-0-2-acetic acid	WO9203132, US 5459150	3/5/1992, 10/17/95	5-LPO inhibitor
Abbott	A-93178					FLAP inhibitor
AstraZeneca	AZD-4407			EP 623614	09/11/94	5-LPO inhibitor

AstraZeneca	ZD-2138		6-((3-Fluoro-5-(tetrahydro-4-methoxy-2H-pyran-4-yl)phenoxy)methyl)-1-methyl-2-(1H)-quinolinone (alternatively NH can be N-methyl)	EP 466452	5-LPO inhibitor
Bayer	BAY-X-1005		(R)-(+)-alpha-cyclopentyl-4-(2-quinolinylmethoxy)-benzeneacetic acid	US 4970215 EP 344519, DE 1980531	FLAP inhibitor
Merck	MK-0591		1-((4-chlorophenyl)methyl)-3-((1,1-dimethylethyl)thio)-alpha, alpha-dimethyl-5-(2-quinolinylmethoxy)-1H-indole-2-propanoic acid	EP 419049, US 19890822	FLAP inhibitor
Merck	MK-866		(3-(3-(4-chlorobenzyl)-3-t-butylthio-5-isopropylindol-2-yl)-2-dimethyl-propanoic acid		5-LPO inhibitor
Merck	MK-886		1-((4-chlorophenyl)methyl)-3-((1,1-dimethylethyl)thio)-alpha, alpha-dimethyl-5-(2-quinolinylmethoxy)-1H-indole-2-propanoic acid	EP 419049, US 19890822	5-LPO inhibitor
Pfizer	CJ-13610		4-(3-(4-(2-Methylimidazol-1-yl)-phenylsulfanyl)-phenyl)-tetrahydro-pyran-4-carboxylic acid amide		5-LPO inhibitor

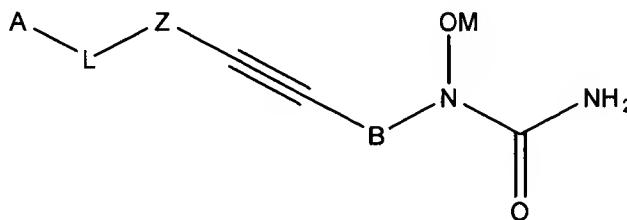
In preferred methods of the invention, the agents set forth in the Agent Table can be used for prophylactic and/or therapeutic treatment for diseases and conditions associated with FLAP or with other members of the leukotriene pathway, or with increased leukotriene synthesis. In particular, they can be used for treatment for myocardial infarction or susceptibility to myocardial infarction, such as for individuals in an at-risk population as described above, (*e.g.*, based on identified risk factors such as elevated cholesterol, elevated C-reactive protein, and/or genotype); for individuals suffering from acute coronary syndrome, such as unstable angina, non-ST-elevation myocardial infarction (NSTEMI) or ST-elevation myocardial infarction (STEMI); methods for reducing risk of MI, stroke or PAOD in persons with asymptomatic ankle/brachial index less than 0.9; for decreasing risk of a subsequent myocardial infarction, such as in individuals who have already had one or more myocardial infarctions; for stroke or susceptibility to stroke; for decreasing risk of a second stroke; for PAOD or susceptibility to PAOD; for treatment of atherosclerosis, such as in patients requiring treatment (*e.g.*, angioplasty, stents, revascularization procedure) to restore blood flow in arteries (*e.g.*, coronary, carotid, and/or femoral arteries); for treatment of asymptomatic ankle/brachial index of less than 0.9; and/or for decreasing leukotriene synthesis (*e.g.*, for treatment of myocardial infarction, ACS, stroke or PAOD

In one preferred embodiment of the invention, the leukotriene synthesis inhibitor is an inhibitor of FLAP such as 1-((4-chlorophenyl)methyl)-3-((1,1-dimethylethyl)thio)- $\alpha,\alpha$ -dimethyl-5-(2-quinolinylmethoxy)-1H-Indole-2-propanoic acid otherwise known as MK-0591, (R)-(+)- $\alpha$ -cyclopentyl-4-(2-quinolinylmethoxy)-Benzeneacetic acid otherwise known as BAY-x-1005, 3-(3-(1,1-dimethylethylthio-5-(quinoline-2-ylmethoxy)-1-(4-chloromethylphenyl)indole-2-yl)-2,2-dimethylpropionaldehyde oxime-0-2-acetic acid otherwise known as A-81834, their optically pure enantiomers, salts, chemical derivatives, analogues, or other compounds inhibiting FLAP that effectively decrease leukotriene biosynthesis when administered to humans.

In another preferred embodiment of the invention, the leukotriene synthesis inhibitor is an inhibitor of 5LO such as zileuton, atreleuton, 6-((3-fluoro-5-(tetrahydro-4-methoxy-2H-pyran-4yl)phenoxy)methyl)-1-methyl-2(1H)-quinolinone

otherwise known as ZD-2138, 1-((4-chlorophenyl)methyl)-3-  
 ((1,1dimethylethylthio)-alpha,alpha-dimethyl-5-( 2-quinolinylmethoxy)-1H-Indole-  
 2-propanoic acid otherwise known as MK-886, 4-(3-(4-(2-Methyl-imidazol-1-yl)-  
 phenylsulfanyl)-phenyl)-tetrahydro-pyran-4-carboxylic acid amide otherwise known  
 5 as CJ-13610, their optically pure enantiomers, salts, chemical derivatives, analogues  
 or other compounds inhibiting 5-LO that effectively decrease leukotriene biosynthesis  
 when administered to humans.

The compound can be represented by the following formula:

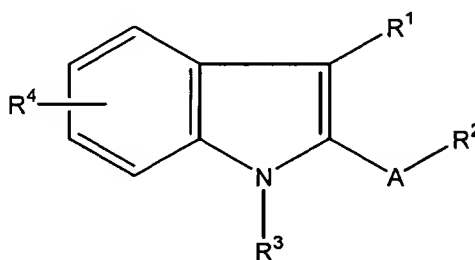


10

or a pharmaceutically acceptable salt thereof, wherein M is selected from the group  
 consisting of hydrogen, a pharmaceutically acceptable cation, and a  
 15 pharmaceutically acceptable metabolically cleavable group; B is a straight or  
 branched divalent alkylene group of from one to twelve carbon atoms; Z is  
 thiazolyl, optionally substituted with alkyl of from one to six carbon atoms or  
 haloalkyl of from one to six carbon atoms; L is selected from the group consisting  
 of (a) alkylene of from 1-6 carbon atoms, (b) alkenylene of from 2-6 carbon atoms,  
 20 (c) alkynylene of from 2-6 carbon atoms, (d) hydroxyalkyl of 1-6 carbon atoms, (e)  
 $>C=O$ , (f)  $>C=N-OR_1$ , where  $R_1$  is hydrogen or  $C_1$ - $C_6$  alkyl, (g)  $-(CHR_1)_n$   
 $(CO)(CHR_2)_m$ , where n and m are independently selected from an integer from one  
 to six and  $R_1$  and  $R_2$  are independently selected from hydrogen and  $C_1$ - $C_6$ -alkyl,  
 (h)  $-(CHR_1)_n C=NOR_2$ , where  $R_1$ ,  $R_2$  and n are as defined above; (i)  $-(CHR_1)_n$   
 25  $ON=CR_2$ , where  $R_1$ ,  $R_2$  and n are as: defined above; (j)  $-(CHR_1)_n -O-(CHR_2)_m -$ ,  
 where  $R_1$ ,  $R_2$ , n and m are as defined above, (k)  $-(CHR_1)_n -NR_2 (CHR_3)_m -$ , where  
 $R_1$ ,  $R_2$ , n and m are as defined above and  $R_3$  is selected from hydrogen and  $C_1$ - $C_6$ -  
 alkyl; (l)  $-(CHR_1)_n -S- CHR_2)_m -$ , where  $R_1$ ,  $R_2$ , n and m are as defined above; and

(m)  $-(\text{CHR}_1)_n-(\text{SO}_2)-(\text{CHR}_2)_m-$ , where  $\text{R}_1$ ,  $\text{R}_2$ ,  $n$  and  $m$  are as defined above; A is carbocyclic aryl optionally substituted with alkyl of from one to six carbon atoms, haloalkyl of from one to six carbon atoms, hydroxyalkyl of from one to six carbon atoms, alkoxy of from one to twelve carbon atoms, alkoxyalkoxyl in which the two  
 5 alkoxy portions may each independently contain from one to six carbon atoms, alkylthio of from one to six carbon atoms, hydroxy, halogen, cyano, amino, alkylamino of from one to six carbon atoms, dialkylamino in which the two alkyl groups may independently contain from one to six carbon atoms, alkanoylamino of from two to eight carbon atoms, N-alkanoyl-N-alkylamino in which the alkanoyl is  
 10 of from two to eight carbon atoms and the alkyl group is of from one to six carbon atoms, alkylaminocarbonyl of from two to eight carbon atoms, dialkylaminocarbonyl in which the two alkyl groups are independently of from one to six carbon atoms, carboxyl, alkoxy carbonyl or from two to eight carbon atoms, phenyl, optionally substituted with alkyl of from one to six carbon atoms, haloalkyl  
 15 of from one to six carbon atoms, alkoxy of from one to six carbon atoms, hydroxy or halogen, phenoxy, optionally substituted with alkyl of from one to six carbon atoms, haloalkyl of from one to six carbon atoms, alkoxy of from one to six carbon atoms, hydroxy or halogen, and phenylthio, optionally substituted with alkyl of from one to six carbon atoms, haloalkyl of from one to six carbon atoms, alkoxy of  
 20 from one to six carbon atoms, hydroxy or halogen. Preferably, the compound is a compound or pharmaceutically acceptable salt thereof having the name (R)-N-{3-[-5-(4-fluorophenylmethyl)thiazo-2-yl]-1-methyl-2-propynyl}-N-hydroxyurea. See U.S. Patent No. 4,615,596, incorporated herein by reference.

25 The compound is represented by the following formula:

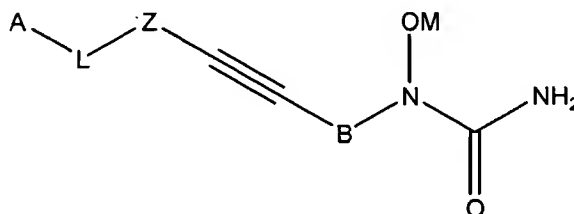


or a pharmaceutically acceptable salt thereof, wherein A is selected from the group consisting of straight or branched divalent alkylene of from one to twelve carbon

atoms and divalent cycloalkylene of from three to eight carbon atoms;  $R_1$  is selected from the group consisting of hydrogen, alkylthio of from one to six carbon atoms, phenylthio, optionally substituted with alkyl of from one to six carbon atoms, alkoxy of from one to six carbon atoms, or halogen, phenylalkylthio in which the alkyl portion contains from one to six carbon atoms, and the phenyl group is optionally substituted with alkyl of from one to six carbon atoms, alkoxy of from one to six carbon atoms, or halogen,  $R_2$  is selected from the group consisting of -COOB wherein B is selected from hydrogen, a pharmaceutically acceptable cation, or a metabolically cleavable group, -COOalkyl where the alkyl portion contains from one to six carbon atoms, -COOalkylcarbocyclicaryl where the alkyl portion contains from one to six carbon atoms and the aryl portion is optionally substituted with alkyl of from one to six carbon atoms, alkoxy of from one to six carbon atoms, or halogen, -CONR<sub>5</sub> R<sub>6</sub> wherein R<sub>5</sub> is selected from the group consisting of hydrogen, hydroxyl, alkyl of from one to six carbon atoms, and alkoxy of from one to six carbon atoms, and R<sub>6</sub> is selected from the group consisting of hydrogen and alkyl of from one to six carbon atoms, -COR<sub>6</sub>, and -OH;  $R_3$  is selected from the group consisting of phenylalkyl in which the alkyl portion contains from one to six carbon atoms, and the phenyl group is optionally substituted with alkyl of from one to six carbon atoms, alkoxy of from one to six carbon atoms, or halogen,  $R_4$  is selected from the group consisting of thiazolylalkyloxy in which the alkyl portion contains from one to six carbon atoms, and the heteroaryl portion is optionally substituted with alkyl of from one to six carbon atoms, alkoxy of from one to six carbon atoms, or halogen, and thiazolyloxy optionally substituted with alkyl of from one to six carbon atoms, alkoxy of from one to six carbon atoms, or halogen.

See U.S. Patent No. 5,288,743, incorporated herein by reference.

The compound can be represented by the formula:



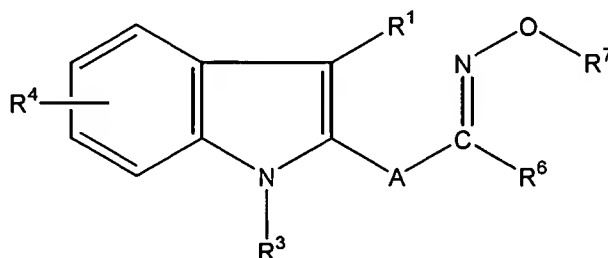


or a pharmaceutically acceptable salt thereof, wherein M is selected from the group consisting of hydrogen, and a pharmaceutically acceptable cation;

- 5 B is a straight or branched divalent alkylene group of from one to twelve carbon atoms; Z is selected from the group consisting of: (a) furyl, optionally substituted with alkyl of from one to six carbon atoms, or haloalkyl of from one to six carbon atoms, and (b) thienyl, optionally substituted with alkyl of from one to six carbon atoms, or haloalkyl of from one to six carbon atoms; and L is alkylene of from 1-6
- 10 carbon atoms; A is phenyl optionally substituted with alkyl of from one to six carbon atoms, haloalkyl of from one to six carbon atoms, hydroxyalkyl of from one to six carbon atoms, alkoxy of from one to twelve carbon atoms, alkoxyalkoxyl in which the two alkoxy portions may each independently contain from one to six carbon atoms, alkylthio of from one to six carbon atoms, hydroxy, halogen, cyano,
- 15 amino, alkylamino of from one to six carbon atoms, dialkylamino in which the two alkyl groups may independently contain from one to six carbon atoms, alkanoylamino of from two to eight carbon atoms, N-alkanoyl-N-alkylamino in which the alkanoyl is of from two to eight carbon atoms and the alkyl group is of from one to six carbon atoms, alkylaminocarbonyl of from two to eight carbon
- 20 atoms, dialkylaminocarbonyl in which the two alkyl groups are independently of from one to six carbon atoms, carboxyl, alkoxycarbonyl of from two to eight carbon atoms, phenyl, optionally substituted with alkyl of from one to six carbon atoms, haloalkyl of from one to six carbon atoms, alkoxy of from one to six carbon atoms, hydroxy or halogen, phenoxy, optionally substituted with alkyl of from one to six
- 25 carbon atoms, haloalkyl of from one to six carbon atoms, alkoxy of from one to six carbon atoms, hydroxy or halogen, or phenylthio, optionally substituted with alkyl of from one to six carbon atoms, haloalkyl of from one to six carbon atoms, alkoxy of from one to six carbon atoms, hydroxy or halogen. Preferably, the compound is a compound or a pharmaceutically acceptable salt thereof selected from the group
- 30 consisting of: N-{3-(5-(4-fluorophenylmethyl)furyl)-3-butyn-2-yl}-N-hydroxyurea; N-{3-(5-(4-fluorophenylmethyl)-2-thienyl)-1-methyl-2-propynyl}-N-hydroxyurea; (R)-N-{3-(5-(4-fluorophenylmethyl)-2-thienyl)-1-methyl-2-

propynyl}-N-hydroxyurea; and (R)-N-{3-(5-(4-chlorophenylmethyl)-2-thienyl)-1-methyl-2-propynyl}-N-hydroxyurea; (S)-N-{3-[5-(4-fluorophenylmethyl)-2-thienyl]-1-methyl-2-propynyl}-N-hydroxyurea. See U.S. Patent No. 5,288,751, incorporated by reference herein.

5        The compound can be represented by the formula:



10        or a pharmaceutically acceptable salt thereof, wherein A is selected from the group consisting of straight or branched divalent alkylene of one to twelve carbon atoms, straight or branched divalent alkenylene of two to twelve carbon atoms, and divalent cycloalkylene of three to eight carbon atoms;  $R^1$  is alkylthio of one to six carbon atoms;  $R^6$  is selected from the group consisting of hydrogen and alkyl of one to six carbon atoms;  $R^7$  is selected from the group consisting of (carboxyl)alkyl in which the alkyl portion is of one to six carbon atoms, (alkoxycarbonyl)alkyl in which the alkoxycarbonyl portion is of two to six carbon atoms and the alkyl portion is of one to six carbon atoms, (aminocarbonyl)alkyl in which the alkyl portion is of one to six carbon atoms, ((alkylamino)carbonyl)alkyl in which each alkyl portion independently is of one to six carbon atoms, and ((dialkylamino)carbonyl)alkyl in which each alkyl portion independently is of one to six carbon atoms;  $R^3$  is phenylalkyl in which the alkyl portion is of one to six carbon atoms;  $R^4$  is 2-, 3- or 6-quinolylmethoxy, optionally substituted with alkyl of one to six carbon atoms, haloalkyl of one to six carbon atoms, alkoxy of one to twelve carbon atoms, halogen, or hydroxy. Preferably, the compound is selected from the group consisting of: 3-(3-1,1-dimethylethylthio)-5-(quinolin-2-ylmethoxy)-1-(4-chlorophenylmethyl)-indol-2-yl)-2,2-dimethylpropionaldehyde oxime-O-2

acetic acid; 3-(3-(1,1-dimethylethylthio)-5-(quinolin-2-ylmethoxy)-1-(4-chloro-phenylmethyl) indol-2-yl)-2,2-dimethylpropionaldehyde oxime-O-2-(3-methyl)butyric acid; 3-(3-(1,1-dimethylethylthio)-5-(6,7-dichloroquinolin-2-ylmethoxy)-1-(4-chlorophenylmethyl) indol-2-yl)-2,2-dimethylpropionaldehyde  
 5 oxime-O-2-acetic acid; and 3-(3-(1,1-dimethylethylthio)-5-(6-fluoroquinolin-2-ylmethoxy)-1-(4chlorophenylmethyl) indol-2-yl)-2,2-dimethylpropionaldehyde oxime-O-2-propionic acid; or a pharmaceutically acceptable salt or ester thereof. See U.S. Patent No. 5,459,150, incorporated by reference herein.

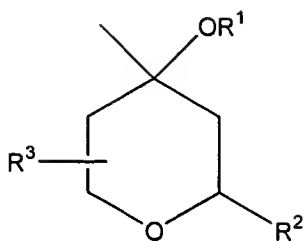
The compound can be represented by the formula:

10

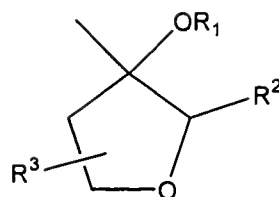


or pharmaceutically acceptable salts thereof, wherein Q is a 9-, 10- or 11-membered bicyclic heterocyclic moiety containing one or two nitrogen heteroatoms  
 15 and optionally containing a further heteroatom selected from nitrogen, oxygen and sulphur, and Q may optionally bear up to four substituents selected from halogeno, hydroxy, cyano, formyl, oxo, thioxo, (1-4C)alkyl, (3-4C)alkenyl, (3-4C)alkynyl, (1-4C)alkoxy, fluoro-(1-4C)alkyl, hydroxy-(1-4C)alkyl, (2-5C)alkanoyl, phenyl, benzoyl and benzyl, and wherein said phenyl, benzoyl and benzyl substituents may  
 20 optionally bear one or two substituents selected from halogeno, (1-4C)alkyl and (1-4C)alkoxy;

X is oxy, thio, sulphinyl or sulphonyl; Ar is phenylene, pyridinediyl, pyrimidinediyl, thiophenediyl, furandiyl, thiazolediyl, oxazolediyl, thiadiazolediyl or oxadiazolediyl which may optionally bear one or two substituents selected from  
 25 halogeno, cyano, trifluoromethyl, hydroxy, amino, (1-4C)alkyl, (1-4C)alkoxy, (1-4C)alkylamino and di-(1-4C)alkylamino; and Q is selected from the groups of the formulae II and III:



II

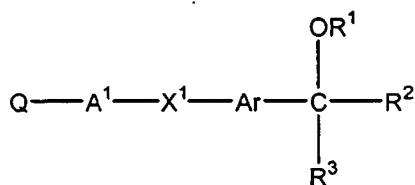


III

wherein R is hydrogen, (2-5C)alkanoyl or benzoyl, and wherein said benzoyl group may optionally bear one or two substituents selected from halogeno, (1-4C)alkyl and (1-4C)alkoxy; R is (1-4C)alkyl; and R is hydrogen or (1-4C)alkyl; or R and R are linked to form a methylene, vinylene, ethylene or trimethylene group. Preferably, the compound is selected from the group consisting of: (2S,4R)-4-[5-fluoro-3-(1-methyl-2-oxo-1,2,3,4-tetrahydroquinolin-6-ylthio)phenyl]-4-hydroxy-2-ethyltetrahydropyran, (2S,4R)-4-[5-fluoro-3-(1-methyl-2-oxo-1,2,3,4-tetrahydroquinolin-6-ylsulphonyl)phenyl]-4-hydroxy-2-methyltetrahydropyran, (2S,4R)-4-hydroxy-2-methyl-4-[2-(1-methyl-2-oxo-1,2,3,4-tetrahydroquinolin-6-ylthio)thiazol-5-yl]tetrahydropyran, (2S,4R)-4-hydroxy-2-methyl-4-[2-(1-methyl-2-oxo-1,2,3,4-tetrahydroquinolin-6-ylsulphonyl)thiazol-5-yl]tetrahydropyran, (2S,4R)-4-[2-(7-fluoro-1-methyl-2-oxo-1,2,3,4-tetrahydroquinolin-6-ylthio)thiazol-5-yl]-4-hydroxy-2-methyltetrahydropyran, (2S,4R)-4-hydroxy-2-methyl-4-[2-(1-methyl-2-oxoindolin-5-ylthio)thiazol-5-yl]tetrahydropyran, (2S,4R)-4-hydroxy-2-methyl-4-[2-(1-methyl-2-oxo-1,2,3,4-tetrahydroquinolin-6-ylthio)thien-4-yl]tetrahydropyran, (2S,4R)-4-hydroxy-2-methyl-4-[2-(1-methyl-2-oxo-1,2,3,4-tetrahydroquinolin-6-ylsulphonyl)thien-4-yl]tetrahydropyran, (2S,4R)-4-hydroxy-2-methyl-4-[2-(1-methyl-2-oxo-1,2,3,4-tetrahydroquinolin-6-ylthio)thien-5-yl]tetrahydropyran, (2S,4R)-4-hydroxy-2-methyl-4-[2-(1-methyl-2-oxo-1,2,3,4-dihydroquinolin-6-ylthio)thien-4-yl]tetrahydropyran, (2S,4R)-4-hydroxy-2-methyl-4-[2-(1,8-dimethyl-2-oxo-1,2,3,4-tetrahydroquinolin-6-ylthio)thien-4-yl]tetrahydropyran, 4-[2-(8-fluoro-1-methyl-2-oxo-1,2,3,4-tetrahydroquinolin-6-ylthio)thien-4-yl]-4-hydroxy-2-methyltetrahydropyran, 4-[2-(7-fluoro-1-methyl-2-oxo-1,2,3,4-tetrahydroquinolin-6-ylthio)thien-4-yl]-4-hydroxy-2-

methyltetrahydropyran, (2S,4R)-4-hydroxy-2-methyl-4-[2-(1-methyl-2-oxoindolin-5-ylthio)thien-4-yl]tetrahydropyran, (2S,4R)-4-hydroxy-2-methyl-4-[3-(1-methyl-2-oxo-1,2,3,4-tetrahydroquinolin-6-ylthio)phenyl]tetrahydropyran, (2S,4R)-4-hydroxy-2-methyl-4-[3-(1-methyl-2-oxo-1,2,3,4-tetrahydroquinolin-6-ylthio)phenyl]tetrahydropyran, (2S,4R)-4-[3-(1-ethyl-2-oxo-1,2,3,4-tetrahydroquinolin-6-ylthio)phenyl]-4-hydroxy-2-methyltetrahydropyran, (2S,4R)-4-[3-(7-fluoro-1-methyl-2-oxo-1,2,3,4-tetrahydroquinolin-6-ylthio)phenyl]-4-hydroxy-2-methyltetrahydropyran, (2S,4R)-4-hydroxy-2-methyl-4-[3-(1-methyl-2-oxo-1,2-dihydroquinolin-6-ylthio)phenyl]tetrahydropyran, (2S,4R)-4-[3-(8-chloro-1-methyl-2-oxo-1,2,3,4-tetrahydroquinolin-6-ylthio)phenyl]-4-hydroxy-2-methyltetrahydropyran and  
 (2S,4R)-4-hydroxy-2-methyl-4-[3-(1-methyl-2-oxoindolin-5-ylthio)phenyl]tetrahydropyran. See EP 623614 B1, incorporated herein by reference.

The compound can be represented by the formula:



wherein Q is a 10-membered bicyclic heterocyclic moiety containing one or two nitrogen heteroatoms which bears one or two thioxo substituents, and which heterocyclic moiety may optionally bear one, two or three further substituents selected from halogeno, hydroxy, cyano, amino, (1-4C)alkyl, (1-4C)alkoxy, fluoro-(1-4C)alkyl, (1-4C)alkylamino, di-[(1-4C)alkyl]amino, amino-(1-4C)alkyl, (1-4C)alkylamino-(1-4C)alkyl, di-[(1-4C)alkyl]amino-(1-4C)alkyl, phenyl and phenyl-(1-4C)alkyl, and wherein said phenyl or phenyl-(1-4C)alkyl substituent may optionally bear a substituent selected from halogeno, (1-4C)alkyl and (1-4C)alkoxy; wherein A is a direct link to X or is (1-3C)alkylene; wherein X is oxy, thio, sulphonyl, sulphonyl or imino; wherein Ar is phenylene which may optionally bear

one or two substituents selected from halogeno, hydroxy, amino, nitro, cyano, carbamoyl, ureido, (1-4C)alkyl, (1-4C)alkoxy, (1-4C)alkylamino, di-[(1-4C)alkyl]amino, fluoro-(1-4C)alkyl and (2-4C)alkanoylamino; or Ar is pyridylene; wherein R is (1-4C)alkyl, (3-4C)alkenyl or (3-4C)alkynyl; and wherein R and R

5 together form a group of the formula -A-X-A- which, together with the carbon atom to which A and A are attached, defines a ring having 5 to 7 ring atoms, wherein A and A, which may be the same or different, each is (1-3C)alkylene and X is oxy, thio, sulphinyl or sulphonyl, and which ring may bear one, two or three substituents, which may be the same or different, selected from hydroxy, (1-

10 4C)alkyl and (1-4C)alkoxy; or wherein R and R together form a group of the formula -A-X-A- which, together with the oxygen atom to which A is attached and with the carbon atom to which A is attached, defines a ring having 5 to 7 ring atoms, wherein A and A, which may be the same or different, each is (1-

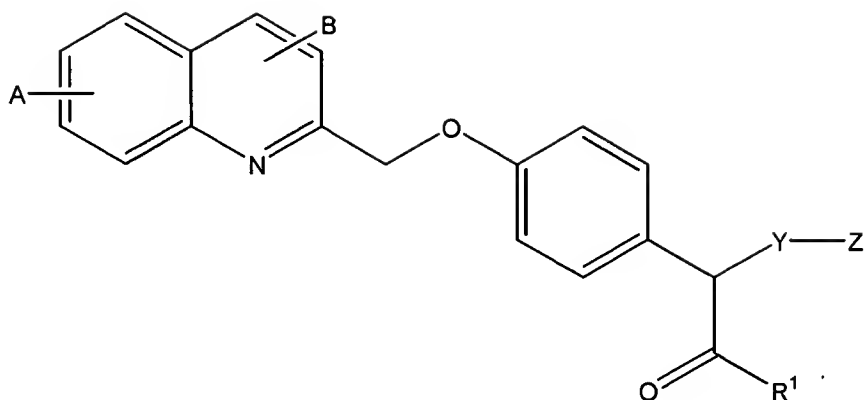
15 3C)alkylene and X is oxy, thio, sulphinyl or sulphonyl, and which ring may bear one, two or three (1-4C)alkyl substituents, and wherein R is (1-4C)alkyl, (2-4C)alkenyl or (2-4C)alkynyl; or a pharmaceutically-acceptable salt thereof. Preferably, the compound is selected from the group consisting of: 4-(5-fluoro-3-(1-methyl-2-thioxo-1,2-dihydroquinolin-6-ylmethoxy)phenyl]-4-

20 ethoxytetrahydropyran and 4-(5-fluoro-3-(1-methyl-2-thioxo-1,2,3,4-tetrahydroquinolin-6-ylmethoxy)phenyl]-4-methoxytetrahydropyran, 4-(5-fluoro-3-(1-methyl-2-thioxo-1,2,3,4-tetrahydroquinolin-6-ylthio)phenyl]-4-methoxytetrahydropyran and pharmaceutically-acceptable salt thereof. See EP 466452 B1, incorporated herein by reference.

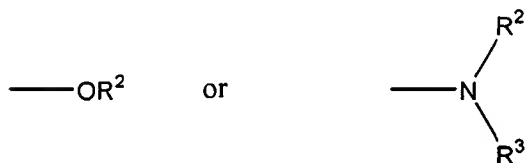
The compound can be a substituted 4-(quinolin-2-ylmethoxy)phenylacetic acid

25 derivative represented by the following formula:

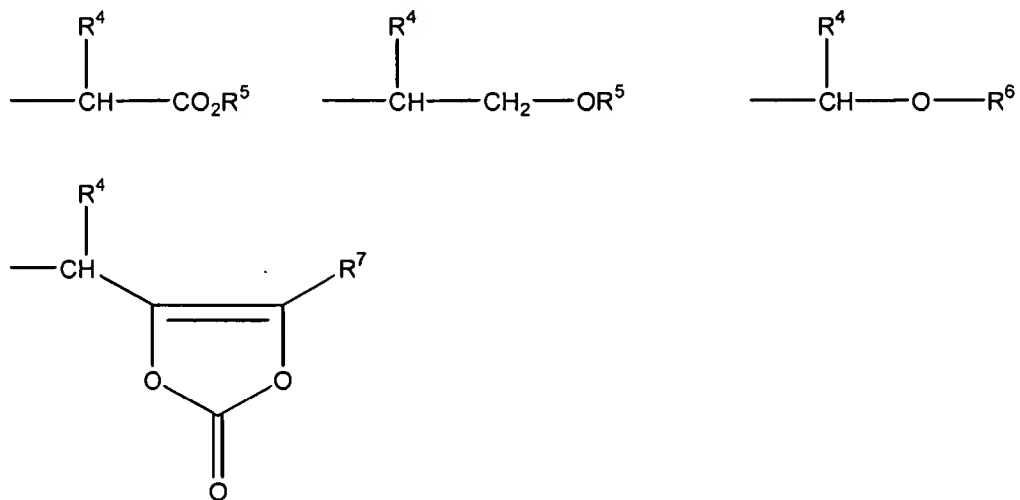
-48-



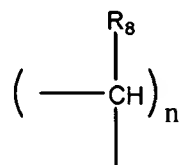
or pharmaceutically acceptable salt thereof, wherein  $R^1$  represents a group of  
 5 the formula:



$R^2$  and  $R^3$  are identical or different and represent hydrogen, lower alkyl, phenyl,  
 10 benzyl or a group of the formula:

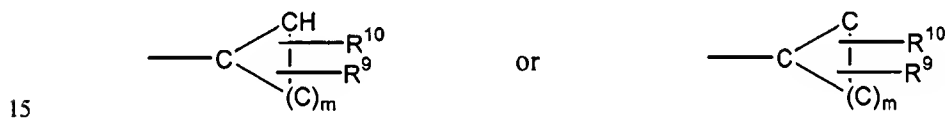


$R^4$  represents hydrogen, lower alkyl, phenyl or benzyl, which can optionally be substituted by hydroxyl, carboxyl, lower alkoxy, carbonyl, lower alkylthio, heteroaryl or carbamoyl,  $R^5$  represents hydrogen, lower alkyl, phenyl or benzyl,  $R^6$  represents a group of the formula  $-COR^5$  or  $-CO^2 R^5$ ,  $R^7$  represents hydrogen, lower alkyl or phenyl, Y represents a group of the formula:



10

wherein  $R^8$  represents hydrogen, lower alkyl or phenyl and n denotes a number of 0 to 5, Z represents norbornyl, or represents a group of the formula:



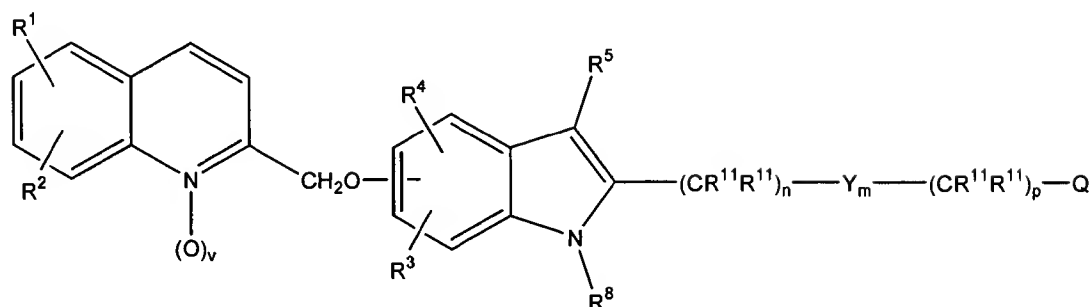
15

wherein  $R^9$  and  $R^{10}$  are identical or different and denote hydrogen, lower alkyl or phenyl, or  $R^9$  and  $R^{10}$  can together form a saturated carbocyclic ring having up to 6 carbon atoms and m denotes a number from 1 to 6, and A and B are identical or different and denote hydrogen, lower alkyl or halogen, or a pharmaceutically acceptable salt thereof. Preferably the compounds are selected from the group consisting of: 2-[4-(quinolin-2-yl-methoxy)phenyl]-2-cyclopentylacetic acid, 2-[4-(quinolin-2-yl-methoxy)phenyl]-2-cyclohexylacetic acid, and 2-[4-(quinolin-2-yl-methoxy)phenyl]-2-cycloheptylacetic acid, (+)-enantiomer of 2-[4-(quinolin-2-yl-methoxy)phenyl]-2-cyclopentylacetic acid, (-)-enantiomer of 2-[4-(quinolin-2-yl-methoxy)phenyl]-2-cyclopentylacetic acid and pharmaceutically acceptable salts thereof. See U.S. Patent No. 4,970,215, incorporated herein by reference.

20  
25



The compound can be represented by the formula:



5

wherein R, R, R, R and R are independently hydrogen, halogen, lower alkyl, lower alkenyl, lower alkynyl, -CF<sub>3</sub>, -CN, -NO<sub>2</sub>, -N<sub>3</sub>, -C(OH)RR, -CO<sub>2</sub>R, -SR, -S(O)R, -S(O)<sub>2</sub>R, -S(O)<sub>2</sub>NRR, -OR, -NRR, -C(O)R or -(CH<sub>2</sub>)tR; R is hydrogen, -CH<sub>3</sub>, -CF<sub>3</sub>, -C(O)H, X-R or X-R; R and R are independently: alkyl, -(CH<sub>2</sub>)uPh(R)<sub>2</sub> or -(CH<sub>2</sub>)uTh(R)<sub>2</sub>; R is -CF<sub>3</sub> or R; R is hydrogen or X-R; each R is independently hydrogen or lower alkyl, or two R's on same carbon atom are joined to form a cycloalkyl ring of 3 to 6 carbon atoms; R is hydrogen, lower alkyl or -CH<sub>2</sub>R;

R is lower alkyl or -(CH<sub>2</sub>)rR; R is -CF<sub>3</sub> or R; R is hydrogen, -C(O)R, R, or two R's on the same nitrogen may be joined to form a monocyclic heterocyclic ring of 4 to 6 atoms containing up to 2 heteroatoms chosen from O, S or N; R is hydrogen, -CF<sub>3</sub>, lower alkyl, lower alkenyl, lower alkynyl or -(CH<sub>2</sub>)rR; R is -(CH<sub>2</sub>)s-C(RR)-(CH<sub>2</sub>)s-R or -CH<sub>2</sub>C(O)NRR; R is hydrogen or lower alkyl; R is a) a monocyclic or bicyclic heterocyclic ring containing from 3 to 9 nuclear carbon atoms and 1 or 2 nuclear hetero-atoms selected from N, S or O and with each ring in the heterocyclic radical being formed of 5 or 6 atoms, or b) the radical W-R; R is alkyl or C(O)R; R is phenyl substituted with 1 or 2 R groups; R is hydrogen, halogen, lower alkyl, lower alkoxy, lower alkylthio, lower alkylsulfonyl, lower alkylcarbonyl, -CF<sub>3</sub>, -CN, -NO<sub>2</sub> or -N<sub>3</sub>; R is alkyl, cycloalkyl, monocyclic monoheterocyclic ring; R is the residual structure of a standard amino acid, or R and R attached to the same

25

N can cyclize to form a proline residue; m is 0 to 1; n is 0 to 3; p is 1 to 3 when m is 1; p is 0 to 3 when m is 0; r is 0 to 2; s is 0 to 3; t is 0 to 2; u is 0 to 3; v is 0 or 1; W is 0, S or NR; X is 0, or NR; X is C(O), CRR, S, S(O) or S(O)<sub>2</sub>; X is C(O), CRR, S(O)<sub>2</sub> or a bond; Y is X or X; Q is -CO<sub>2</sub>R, -C(O)NHS(O)<sub>2</sub>R, -NHS(O)<sub>2</sub>R, -S(O)<sub>2</sub>NHR -C(O)NRR, -CO<sub>2</sub>R, -C(O)NRR, -CH<sub>2</sub>OH, or 1H- or 2H-tetrazol-5-yl; and the pharmaceutically acceptable salts thereof. Preferred embodiments of the compounds are selected from the following and pharmaceutically acceptable salts thereof:

- 10 3-[N-(p-chlorobenzyl)-3-(t-butylthio)-5-(quinolin-2-ylmethoxy)indol-2-yl]-2,2-dimethylpropanoic acid;
- 3-[N-(p-chlorobenzyl)-3-methyl-5-(quinolin-2-ylmethoxy)indol-2-yl]-2,2-dimethylpropanoic acid;
- 3-[N-(p-t-butylthiobenzyl)-3-(t-butylthio)-5-(quinolin-2-ylmethoxy)indol-2-yl]-2,2-dimethylpropanoic acid;
- 15 3-[N-(p-chlorobenzyl)-3-(phenylthio)-5-(quinolin-2-ylmethoxy)indol-2-yl]-2,2-dimethylpropanoic acid;
- 3-[N-(p-chlorobenzyl)-3-(phenylsulfonyl)-5-(quinolin-2-ylmethoxy)indol-2-yl]-2,2-dimethyl propanoic acid, N-oxide;
- 20 3-[N-(p-chlorobenzyl)-3-(phenylsulfonyl)-5-(quinolin-2-ylmethoxy)indol-2-yl]-2,2-dimethylpropanoic acid;
- 3-[N-(p-chlorobenzyl)-3-(phenylsulfinyl)-5-(quinolin-2-ylmethoxy)indol-2-yl]-2,2-dimethylpropanoic acid;
- 3-[N-(p-chlorobenzyl)-5-(quinolin-2-ylmethoxy)indol-2-yl]-2,2-dimethylpropanoic acid;;
- 25 3-[N-(p-chlorobenzyl)-3-benzoyl-5-(quinolin-2-ylmethoxy)indol-2-yl]-2,2-dimethylpropanoic acid;
- 3-[N-(p-chlorobenzyl)-3-benzyl-5-(quinolin-2-ylmethoxy)indol-2-yl]-2,2-dimethylpropanoic acid;
- 30 3-[N-(p-chlorobenzyl)-3-(3,3-dimethyl-1-oxo-1-butyl)-5-(quinolin-2-ylmethoxy)indol-2-yl]-2,2-dimethylpropanoic acid;
- 2-[N-(p-chlorobenzyl)-3-(t-butylthio)-5-(quinolin-2-ylmethoxy)indol-2-

- yl]ethoxyethanoic acid;
- 3-[N-(p-chlorobenzyl)-3-(3,3-dimethyl-1-butyl)-5-(quinolin-2-ylmethoxy)indol-2-yl]-2,2-dimethylpropanoic acid;
- 3-[N-(p-chlorobenzyl)-3-(t-butylthio)-5-(quinolin-2-ylmethoxy)indol-2-yl]-2-methylpropanoic acid;
- 5 3-[N-(p-chlorobenzyl)-3-methyl-5-(6,7-dichloroquinolin-2-ylmethoxy)indol-2-yl]-2,2-dimethylpropanoic acid;
- 3-[N-(p-chlorobenzyl)-3-methyl-5-(7-chloroquinolin-2-ylmethoxy)indol-2-yl]-2,2-dimethylpropanoic acid;
- 10 3-[N-(p-chlorobenzyl)-4-allyl-5-(quinolin-2-ylmethoxy)-3-(t-butylthio)indol-2-yl]-2,2-dimethylpropanoic acid;
- 3-[N-(p-chlorobenzyl)-4-allyl-5-(quinolin-2-ylmethoxy)indol-2-yl]-2,2-dimethylpropanoic acid;
- 3-[N-(p-chlorobenzyl)-6-(quinolin-2-ylmethoxy)-3-(t-butylthio)indol-2-yl]-2,2-dimethylpropanoic acid;
- 15 3-[N-(p-chlorobenzyl)-4-(quinolin-2-ylmethoxy)-3-(t-butylthio)indol-2-yl]-2,2-dimethylpropanoic acid;
- 3-[N-(p-chlorobenzyl)-7-(quinolin-2-ylmethoxy)-3-(t-butylthio)indol-2-yl]-2,2-dimethylpropanoic acid;
- 20 2-[2-[N-(p-chlorobenzyl)-3-(t-butylthio)-5-(quinolin-2-ylmethoxy)indol-2-yl]ethoxy]propanoic acid;
- 3-[N-(p-chlorobenzyl)-4-(quinolin-2-ylmethoxy)indol-2-yl]-2,2-dimethylpropanoic acid;;
- 3-[N-methyl-3-(p-chlorobenzoyl)-6-(quinolin-2-ylmethoxy)indol-2-yl]-2,2-dimethylpropanoic acid,
- 25 3-[N-methyl-3-(p-chlorobenzyl)-6-(quinolin-2-ylmethoxy)indol-2-yl]-2,2-dimethylpropanoic acid,
- 3-[N-(4-chlorobenzyl)-3-i-propoxy-5-(quinolin-2-ylmethoxy)indol-2-yl]-2,2-dimethylpropanoic acid,
- 30 3-[N-(4-chlorobenzyl)-3-(t-butylthio)-5-(quinolin-2-ylmethoxy)indol-2-yl]-2-ethylpropanoic acid,
- 3-[N-(4-chlorobenzyl)-3-trifluoroacetyl-5-(quinolin-2-ylmethoxy)indol-

- 2-yl]-2,2-dimethylpropanoic acid,  
 3-[N-(4-chlorobenzyl)-3-(3,3-dimethyl-1-oxo-1-butyl)-5-(quinolin-2-ylmethoxy)indol-2-yl]-2-methylpropanoic acid,  
 3-[3-(3,3-dimethyl-1-oxo-1-butyl-5-(quinolin-2-ylmethoxy)indol-2-yl]-  
 5 2,2-dimethylpropanoic acid,  
 3-[N-(4-trifluoromethylbenzyl)-3-(3,3-dimethyl-1-oxo-1-butyl)-5-(quinolin-2-yl-methoxy)indol-2-yl]-2,2-dimethylpropanoic acid,  
 3-[N-benzyl-3-(3,3-dimethyl-1-oxo-1-butyl)-5-(quinolin-2-ylmethoxy)indol-2-yl]-2,2-dimethylpropanoic acid,  
 10 3-[N-(3-methoxybenzyl)-3-(3,3-dimethyl-1-oxo-1-butyl)-5-(quinolin-2-ylmethoxy)indol-2-yl]-2,2-dimethylpropanoic acid,  
 3-[N-allyl-3-(3,3-dimethyl-1-oxo-1-butyl)-5-(quinolin-2-ylmethoxy)indol-2-yl]-2,2-dimethylpropanoic acid,  
 3-[N-(4-methoxybenzyl)-3-(3,3-dimethyl-1-oxo-1-butyl)-5-(quinolin-2-ylmethoxy)indol-2-yl]-2,2-dimethylpropanoic acid,  
 15 3-[N-methyl-3-(3,3-dimethyl-1-oxo-3-butyl)-5-(quinolin-2-ylmethoxy)indol-2-yl]-2,2-dimethylpropanoic acid,  
 3-[3-(4-chlorobenzyl)-6-(quinolin-2-ylmethoxy)indol-2-yl]-2,2-dimethylpropanoic acid.  
 20 3-[N-(phenylsulfonyl)-3-(4-chlorobenzyl)-6-(quinolin-2-ylmethoxy)indol-2-yl]-2,2-dimethylpropanoic acid,  
 3-[N-benzyl-3-(4-chlorobenzyl)-6-(quinolin-2-ylmethoxy)indol-2-yl]-2,2-dimethylpropanoic acid,  
 3-[N-(4-chlorobenzyl)-3-(t-butylsulfonyl)-5-(quinolin-2-ylmethoxy)indol-2-yl]-2,2-dimethylpropanoic acid,  
 25 3-[N-(4-chlorobenzyl)-3-(t-butylsulfinyl)-5-(quinolin-2-ylmethoxy)indol-2-yl]-2,2-dimethylpropanoic acid,  
 3-[N-allyl-3-(4-chlorobenzyl)-6-(quinolin-2-ylmethoxy)indol-2-yl]-2,2-dimethylpropanoic acid,  
 30 3-[N-(n-propyl)-3-(4-chlorobenzyl)-6-(quinoline-2-ylmethoxy)indol-2-yl]-2,2-dimethylpropanoic acid,  
 3-[N-ethyl-3-(4-chlorobenzyl)-6-(quinolin-2-ylmethoxy)indol-2-yl]-2,2-

- dimethylpropanoic acid,  
3-[N-(4-chlorobenzyl)-3-(4-t-butylbenzoyl)-5-(quinolin-2-yl-  
methoxy)indol-2-yl]-2,2-dimethylpropanoic acid,  
3-[N-(4-chlorobenzyl)-3-(4-chlorobenzoyl)-5-(quinolin-2-  
ylmethoxy)indol-2-yl]-2,2-dimethylpropanoic acid,  
5 3-[N-(4-chlorobenzyl)-3-(1,1-dimethylethyl)-5-(quinolin-2-  
ylmethoxy)indol-2-yl]-2,2-dimethylpropanoic acid,  
3-[N-(4-chlorobenzyl)-3-acetyl-5-(quinolin-2-ylmethoxy)indol-2-yl]-  
2,2-dimethylpropanoic acid  
10 3-[N-(4-chlorobenzyl)-3-cyclopropanecarbonyl-5-(quinolin-2-  
ylmethoxy)indol-2-yl]-2,2-dimethylpropanoic acid,  
3-[N-(4-chlorobenzyl)-3-(3-cyclopentylpropanoyl)-5-(quinolin-2-  
ylmethoxy)indol-2-yl]-2,2-dimethylpropanoic acid,  
3-[N-(4-chlorobenzyl)-3-(3-methylbutanoyl)-5-(quinolin-2-yl-  
methoxy)indol-2-yl]-2,2-dimethylpropanoic acid,  
15 3-[N-(4-chlorobenzyl)-3-propanoyl-5-(quinolin-2-ylmethoxy)indol-2-  
yl]-2,2-dimethylpropanoic acid,  
3-[N-(4-chlorobenzyl)-3-(2-methylpropanoyl)-5-(quinolin-2-  
ylmethoxy)indol-2-yl]-2,2-dimethylpropanoic acid,  
20 3-[N-(4-chlorobenzyl)-3-trimethylacetyl-5-(quinolin-2-ylmethoxy)indol-  
2-yl]-2,2-dimethylpropanoic acid,  
3-[N-(4-chlorobenzyl)-3-phenylacetyl-5-(quinolin-2-ylmethoxy)indol-2-  
yl]-2,2-dimethylpropanoic acid,  
3-[N-(4-fluorobenzyl)-3-(3,3-dimethyl-1-oxo-1-butyl)-5-(quinolin-2-  
ylmethoxy)indol-2-yl]-2,2-dimethylpropanoic acid,  
25 3-[N-(4-bromobenzyl)-3-(3,3-dimethyl-1-oxo-1-butyl)-5-(quinolin-2-  
ylmethoxy)indol-2-yl]-2,2-dimethylpropanoic acid,  
3-[N-(4-iodobenzyl)-3-(3,3-dimethyl-1-oxo-1-butyl)-5-(quinolin-2-  
ylmethoxy)indol-2-yl]-2,2-dimethylpropanoic acid,  
30 3-[N-(4-chlorobenzyl)-3-(1,1-dimethylbutyl)-5-(quinolin-2-  
ylmethoxy)indol-2-yl]-2,2-dimethylpropanoic acid,  
3-[N-(4-chlorobenzyl)-3-(1,1-dimethylpropyl)-5-(quinolin-2-

- ylmethoxy)indol-2-yl]-2,2-dimethylpropanoic acid,  
 3-[N-(3-fluorobenzyl)-3-(1,1-dimethylethyl)-5-(quinolin-2-ylmethoxy)indol-2-yl]-2,2-dimethylpropanoic acid,  
 3-[N-(4-chlorobenzyl)-3-(3-methylethyl)-5-(quinolin-2-ylmethoxy)indol-2-yl]-2,2-dimethylpropanoic acid,  
 5 3-[N-(4-chlorobenzyl)-3-cyclopropyl-5-(quinolin-2-ylmethoxy)indol-2-yl]-2,2-dimethylpropanoic acid,  
 3-[N-(4-chlorobenzyl)-3-(1-methyl-1-cyclopropyl)-5-(quinolin-2-ylmethoxy)indol-2-yl]-2,2-dimethylpropanoic acid,  
 10 3-[N-(4-chlorobenzyl)-3-cyclopentyl-5-(quinolin-2-ylmethoxy)indol-2-yl]-2,2-dimethylpropanoic acid,  
 3-[N-(4-chlorobenzyl)-3-cyclohexyl-5-(quinolin-2-ylmethoxy)indol-2-yl]-2,2-dimethylpropanoic acid,  
 3-[N-(4-chlorobenzyl)-3-( $\alpha$ ,  $\alpha$ -dimethylbenzyl)-5-(quinolin-2-ylmethoxy)indol-2-yl]-2,2-dimethylpropanoic acid,  
 15 3-[N-(4-chlorobenzyl)-3-(2-{4-chloro- $\alpha$ ,  $\alpha$ -dimethylbenzyl})-5-(quinolin-2-ylmethoxy)indol-2-yl]-2,2-dimethylpropanoic acid,  
 3-[N-(4-chlorobenzyl)-3-(1-adamantyl)-5-(quinolin-2-ylmethoxy)indol-2-yl]-2,2-dimethylpropanoic acid,  
 20 3-[N-(4-chlorobenzyl)-3-((1-adamantyl)methyl)-5-(quinolin-2-ylmethoxy)indol-2-yl]-2,2-dimethylpropanoic acid,  
 3-[N-(1,1-dimethylethyl)-3-(4-chlorobenzyl)-6-(quinolin-2-ylmethoxy)indol-2-yl]-2,2-dimethylpropanoic acid,  
 3-[N-(1,1-dimethylpropyl)-3-(4-chlorobenzyl)-6-(quinoline-2-ylmethoxy)indol-2-yl]-2,2-dimethylpropanoic acid,  
 25 3-[N-(4-chlorobenzyl)-3-(3,3-dimethyl-1-oxo-1-butyl)-5-(quinolin-2-ylmethoxy)indol-2-yl]-2,2-diethylpropanoic acid,  
 methyl 3-[N-(4-chlorobenzyl)-3,6-bis(acetyl)-5-(quinolin-2-ylmethoxy)indol-2-yl]-2,2 dimethyl propanoate or  
 30 methyl 3-[N-(4-chlorobenzyl)-3,6-bis(cyclopropanecarbonyl)-5-(quinolin-2-ylmethoxy)indol-2-yl]-2,2-dimethyl propanoate. See EP 419049 B1, incorporated herein by reference.

The term "alkyl" refers to a monovalent group derived from a straight or branched chain saturated hydrocarbon by the removal of a single hydrogen atom. Alkyl groups are exemplified by methyl, ethyl, n- and iso-propyl, n-, sec-, iso- and tert-butyl, and the like. The term "hydroxyalkyl" represents an alkyl group, as defined above, substituted by one to three hydroxyl groups with the proviso that no more than one hydroxy group may be attached to a single carbon atom of the alkyl group. The term "alkylamino" refers to a group having the structure -NHR' wherein R' is alkyl, as previously defined, examples of alkylamino include methylamino, ethylamino, iso-propylamino and the like.

5 The term "alkylaminocarbonyl" refers to an alkylamino group, as previously defined, attached to the parent molecular moiety through a carbonyl group. Examples of alkylaminocarbonyl include methylamino-carbonyl, ethylaminocarbonyl, iso-propylaminocarbonyl and the like. The term "alkylthio" refers to an alkyl group, as defined above, attached to the parent

10 molecular moiety through a sulfur atom and includes such examples as methylthio, ethylthio, propylthio, n-, sec- and tert-butylthio and the like. The term "alkanoyl" represents an alkyl group, as defined above, attached to the parent molecular moiety through a carbonyl group. Alkanoyl groups are exemplified by formyl, acetyl, propionyl, butanoyl and the like. The term

15 "alkanoylamino" refers to an alkanoyl group, as previously defined, attached to the parent molecular moiety through a nitrogen atom. Examples of alkanoylamino include formamido, acetamido, and the like. The term "N-alkanoyl-N-alkylamino" refers to an alkanoyl group, as previously defined, attached to the parent molecular moiety through an aminoalkyl group. Examples

20 of N-alkanoyl-N-alkylamino include N-methylformamido, N-methyl-acetamido, and the like. The terms "alkoxy" or "alkoxyl" denote an alkyl group, as defined above, attached to the parent molecular moiety through an oxygen atom. Representative alkoxy groups include methoxyl, ethoxyl, propoxyl, butoxyl, and the like. The term "alkoxyalkoxyl" refers to an alkyl group, as defined above,

25 attached through an oxygen to an alkyl group, as defined above, attached in turn through an oxygen to the parent molecular moiety. Examples of alkoxyalkoxyl include methoxymethoxyl, methoxyethoxyl, ethoxyethoxyl and the like. The

30

term "alkoxyalkyl" refers to an alkoxy group, as defined above, attached through an alkylene group to the parent molecular moiety. The term "alkoxycarbonyl" represents an ester group; *i.e.*, an alkoxy group, attached to the parent molecular moiety through a carbonyl group such as

5 methoxycarbonyl, ethoxycarbonyl, and the like. The term "alkenyl" denotes a monovalent group derived from a hydrocarbon containing at least one carbon-carbon double bond by the removal of a single hydrogen atom. Alkenyl groups include, for example, ethenyl, propenyl, butenyl, 1-methyl-2-buten-1-yl and the like. The term "alkylene" denotes a divalent group derived from a straight or

10 branched chain saturated hydrocarbon by the removal of two hydrogen atoms, for example methylene, 1,2-ethylene, 1,1-ethylene, 1,3-propylene, 2,2-dimethylpropylene, and the like. The term "alkenylene" denotes a divalent group derived from a straight or branched chain hydrocarbon containing at least one carbon-carbon double bond. Examples of alkenylene include  $-\text{CH}=\text{CH}-$ , -

15  $\text{CH}_2\text{CH}=\text{CH}-$ ,  $-\text{C}(\text{CH}_3)=\text{CH}-$ ,  $-\text{CH}_2\text{CH}=\text{CHCH}_2-$ , and the like. The term "cycloalkylene" refers to a divalent group derived from a saturated carbocyclic hydrocarbon by the removal of two hydrogen atoms, for example cyclopentylene, cyclohexylene, and the like. The term "cycloalkyl" denotes a monovalent group derived from a monocyclic or bicyclic saturated carbocyclic

20 ring compound by the removal of a single hydrogen atom. Examples include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, bicyclo[2.2.1]heptanyl, and bicyclo[2.2.2]octanyl. The term "alkynylene" refers to a divalent group derived by the removal of two hydrogen atoms from a straight or branched chain acyclic hydrocarbon group containing a carbon-carbon triple bond. Examples of

25 alkynylene include  $-\text{CH}\equiv\text{CH}-$ ,  $-\text{CH}\equiv\text{CH}-\text{CH}_2-$ ,  $-\text{CH}\equiv\text{CH}-\text{CH}(\text{CH}_3)-$ , and the like. The term "carbocyclic aryl" denotes a monovalent carbocyclic ring group derived by the removal of a single hydrogen atom from a monocyclic or bicyclic fused or non-fused ring system obeying the " $4n+2$  p electron" or Huckel aromaticity rule. Examples of carbocyclic aryl groups include phenyl,

30 1- and 2-naphthyl, biphenyl, fluorenyl, and the like. The term "(carbocyclic aryl)alkyl" refers to a carbocyclic aryl ring group as defined above, attached to the parent molecular moiety through an alkylene group. Representative



(carbocyclic aryl)alkyl groups include phenylmethyl, phenylethyl, phenylpropyl, 1-naphthylmethyl, and the like. The term "carbocyclicarylalkoxy" refers to a carbocyclicaryl alkyl group, as defined above, attached to the parent molecular moiety through an oxygen atom. The term "carbocyclic

5 aryloxyalkyl" refers to a carbocyclic aryl group, as defined above, attached to the parent molecular moiety through an oxygen atom and thence through an alkylene group. Such groups are exemplified by phenoxymethyl, 1- and 2-naphthyloxymethyl, phenoxyethyl and the like. The term "(carbocyclic aryl)alkoxyalkyl" denotes a carbocyclic aryl group as defined above, attached to

10 the parent molecular moiety through an alkoxyalkyl group. Representative (carbocyclic aryl)alkoxyalkyl groups include phenylmethoxymethyl, phenylethoxymethyl, 1- and 2-naphthylmethoxyethyl, and the like. "Carbocyclic arylthioalkyl" represents a carbocyclic aryl group as defined above, attached to the parent molecular moiety through a sulfur atom and thence

15 through an alkylene group and are typified by phenylthiomethyl, 1- and 2-naphthylthioethyl and the like. The term "dialkylamino" refers to a group having the structure  $-NR'R''$  wherein  $R'$  and  $R''$  are independently selected from alkyl, as previously defined. Additionally,  $R'$  and  $R''$  taken together may optionally be  $-(CH_2)_{kk}$  -- where  $kk$  is an integer of from 2 to 6. Examples of

20 dialkylamino include, dimethylamino, diethylaminocarbonyl, methylethylamino, piperidino, and the like. The term "halo or halogen" denotes fluorine, chlorine, bromine or iodine. The term "haloalkyl" denotes an alkyl group, as defined above, having one, two, or three halogen atoms attached thereto and is exemplified by such groups as chloromethyl, bromoethyl,

25 trifluoromethyl, and the like. The term "hydroxyalkyl" represents an alkyl group, as defined above, substituted by one to three hydroxyl groups with the proviso that no more than one hydroxy group may be attached to a single carbon atom of the alkyl group. The term "phenoxy" refers to a phenyl group attached to the parent molecular moiety through an oxygen atom. The term "phenylthio"

30 refers to a phenyl group attached to the parent molecular moiety through a sulfur atom. The term "pyridyloxy" refers to a pyridyl group attached to the parent molecular moiety through an oxygen atom. The terms "heteroaryl" or

"heterocyclic aryl" as used herein refers to substituted or unsubstituted 5- or 6-membered ring aromatic groups containing one oxygen atom, one, two, three, or four nitrogen atoms, one nitrogen and one sulfur atom, or one nitrogen and one oxygen atom. The term heteroaryl also includes bi- or tricyclic groups in which the aromatic heterocyclic ring is fused to one or two benzene rings.

Representative heteroaryl groups are pyridyl, thienyl, indolyl, pyrazinyl, isoquinolyl, pyrrolyl, pyrimidyl, benzothienyl, furyl, benzo[b]furyl, imidazolyl, thiazolyl, carbazolyl, and the like. The term "heteroarylalkyl" denotes a heteroaryl group, as defined above, attached to the parent molecular moiety through an alkylene group. The term "heteroaryloxy" denotes a heteroaryl group, as defined above, attached to the parent molecular moiety through an oxygen atom. The term "heteroarylalkoxy" denotes a heteroarylalkyl group, as defined above, attached to the parent molecular moiety through an oxygen atom.

#### NUCLEIC ACID THERAPEUTIC AGENTS

In another embodiment, a nucleic acid of the invention; a nucleic acid complementary to a nucleic acid of the invention; or a portion of such a nucleic acid (*e.g.*, an oligonucleotide as described below); or a nucleic acid encoding a member of the leukotriene pathway (*e.g.*, 5-LO), can be used in "antisense" therapy, in which a nucleic acid (*e.g.*, an oligonucleotide) which specifically hybridizes to the mRNA and/or genomic DNA of a nucleic acid is administered or generated *in situ*. The antisense nucleic acid that specifically hybridizes to the mRNA and/or DNA inhibits expression of the polypeptide encoded by that mRNA and/or DNA, *e.g.*, by inhibiting translation and/or transcription. Binding of the antisense nucleic acid can be by conventional base pair complementarity, or, for example, in the case of binding to DNA duplexes, through specific interaction in the major groove of the double helix.

An antisense construct can be delivered, for example, as an expression plasmid as described above. When the plasmid is transcribed in the cell, it produces RNA that is complementary to a portion of the mRNA and/or DNA that encodes the polypeptide for the member of the leukotriene pathway (*e.g.*,

FLAP or 5-LO). Alternatively, the antisense construct can be an oligonucleotide probe that is generated *ex vivo* and introduced into cells; it then inhibits expression by hybridizing with the mRNA and/or genomic DNA of the polypeptide. In one embodiment, the oligonucleotide probes are modified  
5 oligonucleotides that are resistant to endogenous nucleases, *e.g.*, exonucleases and/or endonucleases, thereby rendering them stable *in vivo*. Exemplary nucleic acid molecules for use as antisense oligonucleotides are phosphoramidate, phosphothioate and methylphosphonate analogs of DNA (see also U.S. Pat. Nos. 5,176,996, 5,264,564 and 5,256,775). Additionally, general approaches to  
10 constructing oligomers useful in antisense therapy are also described, for example, by Van der Krol *et al.* (*Biotechniques* 6:958-976 (1988)); and Stein *et al.* (*Cancer Res.* 48:2659-2668 (1988)). With respect to antisense DNA, oligodeoxyribonucleotides derived from the translation initiation site are preferred.

15 To perform antisense therapy, oligonucleotides (mRNA, cDNA or DNA) are designed that are complementary to mRNA encoding the polypeptide. The antisense oligonucleotides bind to mRNA transcripts and prevent translation. Absolute complementarity, although preferred, is not required. A sequence "complementary" to a portion of an RNA, as referred to  
20 herein, indicates that a sequence has sufficient complementarity to be able to hybridize with the RNA, forming a stable duplex; in the case of double-stranded antisense nucleic acids, a single strand of the duplex DNA may thus be tested, or triplex formation may be assayed. The ability to hybridize will depend on both the degree of complementarity and the length of the antisense nucleic acid,  
25 as described in detail above. Generally, the longer the hybridizing nucleic acid, the more base mismatches with an RNA it may contain and still form a stable duplex (or triplex, as the case may be). One skilled in the art can ascertain a tolerable degree of mismatch by use of standard procedures.

30 The oligonucleotides used in antisense therapy can be DNA, RNA, or chimeric mixtures or derivatives or modified versions thereof, single-stranded or double-stranded. The oligonucleotides can be modified at the base moiety, sugar moiety, or phosphate backbone, for example, to improve stability of the

molecule, hybridization, etc. The oligonucleotides can include other appended groups such as peptides (*e.g.* for targeting host cell receptors *in vivo*), or agents facilitating transport across the cell membrane (see, *e.g.*, Letsinger *et al.*, *Proc. Natl. Acad. Sci. USA* 86:6553-6556 (1989); Lemaitre *et al.*, *Proc. Natl. Acad. Sci. USA* 84:648-652 (1987); PCT International Publication No. WO 88/09810) or the blood-brain barrier (see, *e.g.*, PCT International Publication No. WO 89/10134), or hybridization-triggered cleavage agents (see, *e.g.*, Krol *et al.*, *BioTechniques* 6:958-976 (1988)) or intercalating agents. (See, *e.g.*, Zon, *Pharm.Res.* 5: 539-549 (1988)). To this end, the oligonucleotide may be conjugated to another molecule (*e.g.*, a peptide, hybridization triggered cross-linking agent, transport agent, hybridization-triggered cleavage agent).

The antisense molecules are delivered to cells that express the member of the leukotriene pathway *in vivo*. A number of methods can be used for delivering antisense DNA or RNA to cells; *e.g.*, antisense molecules can be injected directly into the tissue site, or modified antisense molecules, designed to target the desired cells (*e.g.*, antisense linked to peptides or antibodies that specifically bind receptors or antigens expressed on the target cell surface) can be administered systematically. Alternatively, in a preferred embodiment, a recombinant DNA construct is utilized in which the antisense oligonucleotide is placed under the control of a strong promoter (*e.g.*, pol III or pol II). The use of such a construct to transfect target cells in the patient results in the transcription of sufficient amounts of single stranded RNAs that will form complementary base pairs with the endogenous transcripts and thereby prevent translation of the mRNA. For example, a vector can be introduced *in vivo* such that it is taken up by a cell and directs the transcription of an antisense RNA. Such a vector can remain episomal or become chromosomally integrated, as long as it can be transcribed to produce the desired antisense RNA. Such vectors can be constructed by recombinant DNA technology methods standard in the art and described above. For example, a plasmid, cosmid, YAC or viral vector can be used to prepare the recombinant DNA construct that can be introduced directly into the tissue site. Alternatively, viral vectors can be used which selectively

infect the desired tissue, in which case administration may be accomplished by another route (*e.g.*, systemically).

In another embodiment of the invention, small double-stranded interfering RNA (RNA interference (RNAi)) can be used. RNAi is a post-transcription process, in which double-stranded RNA is introduced, and sequence-specific gene silencing results, though catalytic degradation of the targeted mRNA. See, *e.g.*, Elbashir, S.M. *et al.*, *Nature* 411:494-498 (2001); Lee, N.S., *Nature Biotech.* 19:500-505 (2002); Lee, S-K. *et al.*, *Nature Medicine* 8(7):681-686 (2002); the entire teachings of these references are incorporated herein by reference. RNAi is used routinely to investigate gene function in a high throughput fashion or to modulate gene expression in human diseases (Chi *et al.*, *PNAS*, 100 (11):6343-6346 (2003)). Introduction of long double stranded RNA leads to sequence-specific degradation of homologous gene transcripts. The long double stranded RNA is metabolized to small 21-23 nucleotide siRNA (small interfering RNA). The siRNA then binds to protein complex RISC (RNA-induced silencing complex) with dual function helicase. The helicase has RNase activity and is able to unwind the RNA. The unwound siRNA allows an antisense strand to bind to a target. This results in sequence dependent degradation of cognate mRNA. Aside from endogenous RNAi, exogenous RNAi, chemically synthesized or recombinantly produced can also be used. Using non-intronic portions of the FLAP gene, such as corresponding mRNA portions of SEQ ID NO.1, or portions of SEQ ID NO: 3, target regions of the FLAP gene that are accessible for RNAi are targeted and silenced. With this technique it is possible to conduct a RNAi gene walk of the nucleic acids of the FLAP gene and determine the amount of inhibition of the protein product. Thus it is possible to design gene-specific therapeutics by directly targeting the mRNAs of the gene.

Endogenous expression of a member of the leukotriene pathway (*e.g.*, FLAP, 5-LO) can also be reduced by inactivating or “knocking out” the gene or its promoter using targeted homologous recombination (*e.g.*, see Smithies *et al.*, *Nature* 317:230-234 (1985); Thomas & Capecchi, *Cell* 51:503-512 (1987); Thompson *et al.*, *Cell* 5:313-321 (1989)). For example, an altered, non-

functional gene of a member of the leukotriene pathway (or a completely unrelated DNA sequence) flanked by DNA homologous to the endogenous gene (either the coding regions or regulatory regions of the gene) can be used, with or without a selectable marker and/or a negative selectable marker, to transfect  
5 cells that express the gene *in vivo*. Insertion of the DNA construct, via targeted homologous recombination, results in inactivation of the gene. The recombinant DNA constructs can be directly administered or targeted to the required site *in vivo* using appropriate vectors, as described above. Alternatively, expression of non-altered genes can be increased using a similar  
10 method: targeted homologous recombination can be used to insert a DNA construct comprising a non-altered functional gene, or the complement thereof, or a portion thereof, in place of an gene in the cell, as described above. In another embodiment, targeted homologous recombination can be used to insert a DNA construct comprising a nucleic acid that encodes a polypeptide variant  
15 that differs from that present in the cell.

Alternatively, endogenous expression of a member of the leukotriene pathway can be reduced by targeting deoxyribonucleotide sequences complementary to the regulatory region of the member of the leukotriene pathway (*i.e.*, the promoter and/or enhancers) to form triple helical structures  
20 that prevent transcription of the gene in target cells in the body. (See generally, Helene, C., *Anticancer Drug Des.*, 6(6):569-84 (1991); Helene, C. *et al.*, *Ann. N.Y. Acad. Sci.* 660:27-36 (1992); and Maher, L. J., *Bioassays* 14(12):807-15 (1992)). Likewise, the antisense constructs described herein, by antagonizing the normal biological activity of one of the members of the leukotriene  
25 pathway, can be used in the manipulation of tissue, *e.g.*, tissue differentiation, both *in vivo* and *for ex vivo* tissue cultures. Furthermore, the anti-sense techniques (*e.g.*, microinjection of antisense molecules, or transfection with plasmids whose transcripts are anti-sense with regard to a nucleic acid RNA or nucleic acid sequence) can be used to investigate the role of one or more  
30 members of the leukotriene pathway in the development of disease-related conditions. Such techniques can be utilized in cell culture, but can also be used in the creation of transgenic animals.

The therapeutic agents as described herein can be delivered in a composition, as described above, or by themselves. They can be administered systemically, or can be targeted to a particular tissue. The therapeutic agents can be produced by a variety of means, including chemical synthesis; 5 recombinant production; *in vivo* production (*e.g.*, a transgenic animal, such as U.S. Pat. No. 4,873,316 to Meade *et al.*), for example, and can be isolated using standard means such as those described herein. In addition, a combination of any of the above methods of treatment (*e.g.*, administration of non-altered polypeptide in conjunction with antisense therapy targeting altered mRNA for a 10 member of the leukotriene pathway; administration of a first splicing variant in conjunction with antisense therapy targeting a second splicing variant) can also be used.

The invention additionally pertains to use of such therapeutic agents, as described herein, for the manufacture of a medicament for the treatment of MI, 15 ACS, stroke, PAOD and/or atherosclerosis, *e.g.*, using the methods described herein.

#### MONITORING PROGRESS OF TREATMENT

The current invention also pertains to methods of monitoring the 20 response of an individual, such as an individual in one of the target populations described above, to treatment with a leukotriene synthesis inhibitor.

Because the level of inflammatory markers can be elevated in individuals who are in the target populations described above, an assessment of the level of inflammatory markers of the individual both before, and during, 25 treatment with the leukotriene synthesis inhibitor will indicate whether the treatment has successfully decreased production of leukotrienes in the arterial vessel wall or in bone-marrow derived inflammatory cells. For example, in one embodiment of the invention, an individual who is a member of a target population as described above (*e.g.*, an individual at risk for MI, ACS, stroke or 30 PAOD, such as an individual who is at-risk due to a FLAP haplotype) can be assessed for response to treatment with a leukotriene synthesis inhibitor, by examining leukotriene levels or leukotriene metabolite levels in the individual.

Blood, serum, plasma or urinary leukotrienes (*e.g.*, leukotriene E4, cysteinyl leukotriene 1), or *ex vivo* production of leukotrienes (*e.g.*, in blood samples stimulated with a calcium ionophore to produce leukotrienes), or leukotriene metabolites, can be measured before, and during or after treatment with the leukotriene synthesis inhibitor. The leukotriene or leukotriene metabolite level before treatment is compared with the leukotriene or leukotriene metabolite level during or after treatment. The efficacy of treatment is indicated by a decrease in leukotriene production: a level of leukotriene or leukotriene metabolite during or after treatment that is significantly lower than the level of leukotriene or leukotriene metabolite before treatment, is indicative of efficacy. A level that is lower during or after treatment can be shown, for example, by decreased serum or urinary leukotrienes, or decreased *ex vivo* production of leukotrienes, or decreased leukotriene metabolites. A level that is “significantly lower”, as used herein, is a level that is less than the amount that is typically found in control individual(s), or is less in a comparison of disease risk in a population associated with the other bands of measurement (*e.g.*, the mean or median, the highest quartile or the highest quintile) compared to lower bands of measurement (*e.g.*, the mean or median, the other quartiles; the other quintiles).

For example, in one embodiment of the invention, the level of a leukotriene or leukotriene metabolite is assessed in an individual before treatment with a leukotriene synthesis inhibitor; and during or after treatment with the leukotriene synthesis inhibitor, and the levels are compared. A level of the leukotriene or leukotriene metabolite during or after treatment that is significantly lower than the level of the leukotriene or leukotriene metabolite before treatment, is indicative of efficacy of treatment with the leukotriene synthesis inhibitor. In another embodiment, production of a leukotriene or a leukotriene metabolite is stimulated in a first test sample from the individual, using a calcium ionophore, before treatment with a leukotriene synthesis inhibitor, and is also stimulated in a second test sample from the individual, using a calcium ionophore, during or after treatment with the leukotriene synthesis inhibitor, and the level of production in the first test sample is compared with the level of production of the leukotriene or leukotriene



metabolite in the second test sample. A level of the leukotriene or leukotriene metabolite in the second test sample that is significantly lower than the level of the leukotriene or leukotriene metabolite in the first test sample, is indicative of efficacy of treatment with the leukotriene synthesis inhibitor.

5           In another embodiment of the invention, an individual who is a member of a target population of individuals at risk for MI, ACS, stroke or PAOD (*e.g.*, an individual in a target population described above, such as an individual at-risk due to elevated C-reactive protein) can be assessed for response to treatment with a leukotriene synthesis inhibitor, by examining levels of  
10       inflammatory markers in the individual. For example, levels of an inflammatory marker in an appropriate test sample (*e.g.*, serum, plasma or urine) can be measured before, and during or after treatment with the leukotriene synthesis inhibitor. The level of the inflammatory marker before treatment is compared with the level of the inflammatory marker during or after  
15       treatment. The efficacy of treatment is indicated by a decrease in the level of the inflammatory marker, that is, a level of the inflammatory marker during or after treatment that is significantly lower (*e.g.*, significantly lower), than the level of inflammatory marker before treatment, is indicative of efficacy. Representative inflammatory markers include: C-reactive protein (CRP), serum  
20       amyloid A, fibrinogen, a leukotriene (*e.g.*, LTB<sub>4</sub>, LTC<sub>4</sub>, LTD<sub>4</sub>, LTE<sub>4</sub>), a leukotriene metabolite, interleukin-6, tissue necrosis factor-alpha, soluble vascular cell adhesion molecules (sVCAM), soluble intervascular adhesion molecules (sICAM), E-selectin, matrix metalloprotease type-1, matrix metalloprotease type-2, matrix metalloprotease type-3, matrix metalloprotease  
25       type-9, myeloperoxidase (MPO), and N-tyrosine. In a preferred embodiment, the marker is CRP or MPO.

#### ASSESSMENT OF INCREASED RISK

30           The present invention additionally pertains to methods for assessing an individual (*e.g.*, an individual who is in a target population as described herein, such as an individual who is at risk for MI, ACS, stroke or PAOD), for an increased risk of MI, ACS, atherosclerosis, stroke, transient ischemic attack, transient monocular blindness, asymptomatic carotid stenosis, PAOD,

claudication, or limb ischemia. The methods comprise assessing the level of a leukotriene metabolite (*e.g.*, LTE<sub>4</sub>, LTD<sub>4</sub>, LTB<sub>4</sub>) in the individual, wherein an increased level of leukotriene metabolite is indicative of an increased risk. The level can be measured in any appropriate tissue or fluid sample, such as blood, serum, plasma, or urine. In one particular embodiment, the sample comprises neutrophils. The level of the leukotriene metabolite can be measured by standard methods, such as the methods described herein. For example, in one embodiment, production of a leukotriene metabolite is stimulated in a first test sample from the individual, using a calcium ionophore. The level of production is compared with a control level. The control level is a level that is typically found in control individual(s), such as individual who are not at risk for MI, ACS, stroke or PAOD; alternatively, a control level is the level that is found by comparison of disease risk in a population associated with the lowest band of measurement (*e.g.*, below the mean or median, the lowest quartile or the lowest quintile) compared to higher bands of measurement (*e.g.*, above the mean or median, the second, third or fourth quartile; the second, third, fourth or fifth quintile). A level of production of the leukotriene metabolite that is significantly greater than the control level, is indicative of an increased risk. Individuals at increased risk are candidates for treatments described herein.

20

## PHARMACEUTICAL COMPOSITIONS

The present invention also pertains to pharmaceutical compositions comprising agents described herein, for example, an agent that is a leukotriene synthesis inhibitor as described herein. For instance, a leukotriene synthesis inhibitor can be formulated with a physiologically acceptable carrier or excipient to prepare a pharmaceutical composition. The carrier and composition can be sterile. The formulation should suit the mode of administration.

Suitable pharmaceutically acceptable carriers include but are not limited to water, salt solutions (*e.g.*, NaCl), saline, buffered saline, alcohols, glycerol, ethanol, gum arabic, vegetable oils, benzyl alcohols, polyethylene glycols,

30

gelatin, carbohydrates such as lactose, amylose or starch, dextrose, magnesium stearate, talc, silicic acid, viscous paraffin, perfume oil, fatty acid esters, hydroxymethylcellulose, polyvinyl pyrrolidone, etc., as well as combinations thereof. The pharmaceutical preparations can, if desired, be mixed with  
5 auxiliary agents, *e.g.*, lubricants, preservatives, stabilizers, wetting agents, emulsifiers, salts for influencing osmotic pressure, buffers, coloring, flavoring and/or aromatic substances and the like which do not deleteriously react with the active agents.

The composition, if desired, can also contain minor amounts of wetting  
10 or emulsifying agents, or pH buffering agents. The composition can be a liquid solution, suspension, emulsion, tablet, pill, capsule, sustained release formulation, or powder. The composition can be formulated as a suppository, with traditional binders and carriers such as triglycerides. Oral formulation can include standard carriers such as pharmaceutical grades of mannitol, lactose,  
15 starch, magnesium stearate, polyvinyl pyrrolidone, sodium saccharine, cellulose, magnesium carbonate, etc.

Methods of introduction of these compositions include, but are not limited to, intradermal, intramuscular, intraperitoneal, intraocular, intravenous, subcutaneous, topical, oral and intranasal. Other suitable methods of  
20 introduction can also include gene therapy (as described below), rechargeable or biodegradable devices, particle acceleration devices ("gene guns") and slow release polymeric devices. The pharmaceutical compositions of this invention can also be administered as part of a combinatorial therapy with other agents.

The composition can be formulated in accordance with the routine  
25 procedures as a pharmaceutical composition adapted for administration to human beings. For example, compositions for intravenous administration typically are solutions in sterile isotonic aqueous buffer. Where necessary, the composition may also include a solubilizing agent and a local anesthetic to ease pain at the site of the injection. Generally, the ingredients are supplied either  
30 separately or mixed together in unit dosage form, for example, as a dry lyophilized powder or water free concentrate in a hermetically sealed container such as an ampule or sachette indicating the quantity of active agent. Where the

composition is to be administered by infusion, it can be dispensed with an infusion bottle containing sterile pharmaceutical grade water, saline or dextrose/water. Where the composition is administered by injection, an ampule of sterile water for injection or saline can be provided so that the ingredients  
5 may be mixed prior to administration.

For topical application, nonsprayable forms, viscous to semi-solid or solid forms comprising a carrier compatible with topical application and having a dynamic viscosity preferably greater than water, can be employed. Suitable formulations include but are not limited to solutions, suspensions, emulsions,  
10 creams, ointments, powders, enemas, lotions, sols, liniments, salves, aerosols, etc., which are, if desired, sterilized or mixed with auxiliary agents, *e.g.*, preservatives, stabilizers, wetting agents, buffers or salts for influencing osmotic pressure, etc. The agent may be incorporated into a cosmetic formulation. For topical application, also suitable are sprayable aerosol preparations wherein the  
15 active ingredient, preferably in combination with a solid or liquid inert carrier material, is packaged in a squeeze bottle or in admixture with a pressurized volatile, normally gaseous propellant, *e.g.*, pressurized air.

Agents described herein can be formulated as neutral or salt forms. Pharmaceutically acceptable salts include those formed with free amino groups  
20 such as those derived from hydrochloric, phosphoric, acetic, oxalic, tartaric acids, etc., and those formed with free carboxyl groups such as those derived from sodium, potassium, ammonium, calcium, ferric hydroxides, isopropylamine, triethylamine, 2-ethylamino ethanol, histidine, procaine, etc.

The agents are administered in a therapeutically effective amount. The  
25 amount of agents which will be therapeutically effective in the treatment of a particular disorder or condition will depend on the nature of the disorder or condition, and can be determined by standard clinical techniques. In addition, *in vitro* or *in vivo* assays may optionally be employed to help identify optimal dosage ranges. The precise dose to be employed in the formulation will also  
30 depend on the route of administration, and the seriousness of the symptoms, and should be decided according to the judgment of a practitioner and each patient's

circumstances. Effective doses may be extrapolated from dose-response curves derived from *in vitro* or animal model test systems.

The invention also provides a pharmaceutical pack or kit comprising one or more containers filled with one or more of the ingredients of the pharmaceutical compositions of the invention. Optionally associated with such container(s) can be a notice in the form prescribed by a governmental agency regulating the manufacture, use or sale of pharmaceuticals or biological products, which notice reflects approval by the agency of manufacture, use of sale for human administration. The pack or kit can be labeled with information regarding mode of administration, sequence of drug administration (*e.g.*, separately, sequentially or concurrently), or the like. The pack or kit may also include means for reminding the patient to take the therapy. The pack or kit can be a single unit dosage of the combination therapy or it can be a plurality of unit dosages. In particular, the agents can be separated, mixed together in any combination, present in a single vial or tablet. Agents assembled in a blister pack or other dispensing means is preferred. For the purpose of this invention, unit dosage is intended to mean a dosage that is dependent on the individual pharmacodynamics of each agent and administered in FDA approved dosages in standard time courses.

## NUCLEIC ACIDS OF THE INVENTION

### *FLAP Nucleic Acids, Portions and Variants*

In addition, the invention pertains to isolated nucleic acid molecules comprising a human FLAP nucleic acid. The term, "FLAP nucleic acid," as used herein, refers to an isolated nucleic acid molecule encoding FLAP polypeptide. The FLAP nucleic acid molecules of the present invention can be RNA, for example, mRNA, or DNA, such as cDNA and genomic DNA. DNA molecules can be double-stranded or single-stranded; single stranded RNA or DNA can be either the coding, or sense strand or the non-coding, or antisense strand. The nucleic acid molecule can include all or a portion of the coding sequence of the gene or nucleic acid and can further comprise additional non-

coding sequences such as introns and non-coding 3' and 5' sequences (including regulatory sequences, for example, as well as promoters, transcription enhancement elements, splice donor/acceptor sites, etc.).

For example, a FLAP nucleic acid can consist of SEQ ID NOs: 1 or 3 or  
5 the complement thereof, or to a portion or fragment of such an isolated nucleic acid molecule (*e.g.*, cDNA or the nucleic acid) that encodes FLAP polypeptide (*e.g.*, a polypeptide such as SEQ ID NO: 2). In a preferred embodiment, the isolated nucleic acid molecule comprises a nucleic acid molecule selected from the group consisting of SEQ ID NOs: 1 or 3, or their complement thereof.

10 Additionally, the nucleic acid molecules of the invention can be fused to a marker sequence, for example, a sequence that encodes a polypeptide to assist in isolation or purification of the polypeptide. Such sequences include, but are not limited to, those that encode a glutathione-S-transferase (GST) fusion protein and those that encode a hemagglutinin A (HA) polypeptide marker from  
15 influenza.

An "isolated" nucleic acid molecule, as used herein, is one that is separated from nucleic acids that normally flank the gene or nucleic acid sequence (as in genomic sequences) and/or has been completely or partially purified from other transcribed sequences (*e.g.*, as in an RNA library). For  
20 example, an isolated nucleic acid of the invention may be substantially isolated with respect to the complex cellular milieu in which it naturally occurs, or culture medium when produced by recombinant techniques, or chemical precursors or other chemicals when chemically synthesized. In some instances, the isolated material will form part of a composition (for example, a crude  
25 extract containing other substances), buffer system or reagent mix. In other circumstances, the material may be purified to essential homogeneity, for example as determined by PAGE or column chromatography such as HPLC. In certain embodiments, an isolated nucleic acid molecule comprises at least about 50, 80 or 90% (on a molar basis) of all macromolecular species present. With  
30 regard to genomic DNA, the term "isolated" also can refer to nucleic acid molecules that are separated from the chromosome with which the genomic DNA is naturally associated. For example, the isolated nucleic acid molecule

can contain less than about 5 kb, including but not limited to 4 kb, 3 kb, 2 kb, 1 kb, 0.5 kb or 0.1 kb of nucleotides which flank the nucleic acid molecule in the genomic DNA of the cell from which the nucleic acid molecule is derived.

5 The nucleic acid molecule can be fused to other coding or regulatory sequences and still be considered isolated. Thus, recombinant DNA contained in a vector is included in the definition of "isolated" as used herein. Also, isolated nucleic acid molecules include recombinant DNA molecules in heterologous host cells, as well as partially or substantially purified DNA molecules in solution. "Isolated" nucleic acid molecules also encompass *in vivo* and *in vitro* RNA transcripts of the DNA molecules of the present invention. 10 An isolated nucleic acid molecule or nucleic acid sequence can include a nucleic acid molecule or nucleic acid sequence that is synthesized chemically or by recombinant means. Therefore, recombinant DNA contained in a vector is included in the definition of "isolated" as used herein. Also, isolated nucleotide sequences include recombinant DNA molecules in heterologous organisms, as well as partially or substantially purified DNA molecules in solution. *In vivo* and *in vitro* RNA transcripts of the DNA molecules of the present invention are also encompassed by "isolated" nucleotide sequences. Such isolated nucleotide sequences are useful in the manufacture of the encoded polypeptide, as probes 15 for isolating homologous sequences (*e.g.*, from other mammalian species), for gene mapping (*e.g.*, by *in situ* hybridization with chromosomes), or for detecting expression of the nucleic acid in tissue (*e.g.*, human tissue), such as by Northern blot analysis. 20

The present invention also pertains to nucleic acid molecules which are not necessarily found in nature but which encode a FLAP polypeptide (*e.g.*, a 25 polypeptide having an amino acid sequence comprising an amino acid sequence of SEQ ID NOs: 2), or another splicing variant of a FLAP polypeptide or polymorphic variant thereof. Thus, for example, DNA molecules that comprise a sequence that is different from the naturally occurring nucleic acid sequence but which, due to the degeneracy of the genetic code, encode a FLAP polypeptide of the present invention are also the 30 subjects of this invention. The invention also encompasses nucleotide

sequences encoding portions (fragments), or encoding variant polypeptides such as analogues or derivatives of a FLAP polypeptide. Such variants can be naturally occurring, such as in the case of allelic variation or single nucleotide polymorphisms, or non-naturally-occurring, such as those induced by various mutagens and mutagenic processes. Intended variations include, but are not limited to, addition, deletion and substitution of one or more nucleotides that can result in conservative or non-conservative amino acid changes, including additions and deletions. Preferably the nucleotide (and/or resultant amino acid) changes are silent or conserved; that is, they do not alter the characteristics or activity of a FLAP polypeptide. In one preferred embodiment, the nucleotide sequences are fragments that comprise one or more polymorphic microsatellite markers. In another preferred embodiment, the nucleotide sequences are fragments that comprise one or more single nucleotide polymorphisms in a FLAP nucleic acid (*e.g.*, the single nucleotide polymorphisms set forth in Table 13, below).

Other alterations of the nucleic acid molecules of the invention can include, for example, labeling, methylation, internucleotide modifications such as uncharged linkages (*e.g.*, methyl phosphonates, phosphotriesters, phosphoamidates, carbamates), charged linkages (*e.g.*, phosphorothioates, phosphorodithioates), pendent moieties (*e.g.*, polypeptides), intercalators (*e.g.*, acridine, psoralen), chelators, alkylators, and modified linkages (*e.g.*, alpha anomeric nucleic acids). Also included are synthetic molecules that mimic nucleic acid molecules in the ability to bind to a designated sequence via hydrogen bonding and other chemical interactions. Such molecules include, for example, those in which peptide linkages substitute for phosphate linkages in the backbone of the molecule.

The invention also pertains to nucleic acid molecules that hybridize under high stringency hybridization conditions, such as for selective hybridization, to a nucleic acid sequence described herein (*e.g.*, nucleic acid molecules which specifically hybridize to a nucleic acid sequence encoding polypeptides described herein, and, optionally, have an activity of the polypeptide). In one embodiment, the invention includes variants described



herein which hybridize under high stringency hybridization conditions (*e.g.*, for selective hybridization) to a nucleic acid sequence comprising a nucleic acid sequence selected from the group consisting of SEQ ID NOs: 1 or 3 or the complement thereof. In another embodiment, the invention includes variants  
5 described herein which hybridize under high stringency hybridization conditions (*e.g.*, for selective hybridization) to a nucleic acid sequence encoding an amino acid sequence of SEQ ID NO: 2 or a polymorphic variant thereof. In a preferred embodiment, the variant that hybridizes under high stringency hybridizations has an activity of a FLAP.

10           Such nucleic acid molecules can be detected and/or isolated by specific hybridization (*e.g.*, under high stringency conditions). “Specific hybridization,” as used herein, refers to the ability of a first nucleic acid to hybridize to a second nucleic acid in a manner such that the first nucleic acid does not hybridize to any nucleic acid other than to the second nucleic acid (*e.g.*, when  
15 the first nucleic acid has a higher similarity to the second nucleic acid than to any other nucleic acid in a sample wherein the hybridization is to be performed). “Stringency conditions” for hybridization is a term of art which refers to the incubation and wash conditions, *e.g.*, conditions of temperature and buffer concentration, which permit hybridization of a particular nucleic acid to a  
20 second nucleic acid; the first nucleic acid may be perfectly (*i.e.*, 100%) complementary to the second, or the first and second may share some degree of complementarity that is less than perfect (*e.g.*, 70%, 75%, 85%, 95%). For example, certain high stringency conditions can be used which distinguish perfectly complementary nucleic acids from those of less complementarity.  
25 “High stringency conditions”, “moderate stringency conditions” and “low stringency conditions” for nucleic acid hybridizations are explained on pages 2.10.1-2.10.16 and pages 6.3.1-6.3.6 in *Current Protocols in Molecular Biology* (Ausubel, F.M. *et al.*, “*Current Protocols in Molecular Biology*”, John Wiley & Sons, (1998), the entire teachings of which are incorporated by reference  
30 herein). The exact conditions which determine the stringency of hybridization depend not only on ionic strength (*e.g.*, 0.2X SSC, 0.1X SSC), temperature (*e.g.*, room temperature, 42°C, 68°C) and the concentration of destabilizing

agents such as formamide or denaturing agents such as SDS, but also on factors such as the length of the nucleic acid sequence, base composition, percent mismatch between hybridizing sequences and the frequency of occurrence of subsets of that sequence within other non-identical sequences. Thus, equivalent  
5 conditions can be determined by varying one or more of these parameters while maintaining a similar degree of identity or similarity between the two nucleic acid molecules. Typically, conditions are used such that sequences at least about 60%, at least about 70%, at least about 80%, at least about 90% or at least about 95% or more identical to each other remain hybridized to one another.  
10 By varying hybridization conditions from a level of stringency at which no hybridization occurs to a level at which hybridization is first observed, conditions which will allow a given sequence to hybridize (*e.g.*, selectively) with the most similar sequences in the sample can be determined.

Exemplary conditions are described in Krause, M.H. and S.A. Aaronson,  
15 *Methods in Enzymology* 200: 546-556 (1991), and in, Ausubel, *et al.*, "*Current Protocols in Molecular Biology*", John Wiley & Sons, (1998), which describes the determination of washing conditions for moderate or low stringency conditions. Washing is the step in which conditions are usually set so as to determine a minimum level of complementarity of the hybrids. Generally,  
20 starting from the lowest temperature at which only homologous hybridization occurs, each °C by which the final wash temperature is reduced (holding SSC concentration constant) allows an increase by 1% in the maximum extent of mismatching among the sequences that hybridize. Generally, doubling the concentration of SSC results in an increase in  $T_m$  of -17°C. Using these  
25 guidelines, the washing temperature can be determined empirically for high, moderate or low stringency, depending on the level of mismatch sought.

For example, a low stringency wash can comprise washing in a solution containing 0.2X SSC/0.1% SDS for 10 minutes at room temperature; a moderate stringency wash can comprise washing in a prewarmed solution  
30 (42°C) solution containing 0.2X SSC/0.1% SDS for 15 minutes at 42°C; and a high stringency wash can comprise washing in prewarmed (68°C) solution containing 0.1X SSC/0.1%SDS for 15 minutes at 68°C. Furthermore, washes

can be performed repeatedly or sequentially to obtain a desired result as known in the art. Equivalent conditions can be determined by varying one or more of the parameters given as an example, as known in the art, while maintaining a similar degree of identity or similarity between the target nucleic acid molecule and the primer or probe used.

The percent homology or identity of two nucleotide or amino acid sequences can be determined by aligning the sequences for optimal comparison purposes (*e.g.*, gaps can be introduced in the sequence of a first sequence for optimal alignment). The nucleotides or amino acids at corresponding positions are then compared, and the percent identity between the two sequences is a function of the number of identical positions shared by the sequences (*i.e.*, % identity = # of identical positions/total # of positions x 100). When a position in one sequence is occupied by the same nucleotide or amino acid residue as the corresponding position in the other sequence, then the molecules are homologous at that position. As used herein, nucleic acid or amino acid “homology” is equivalent to nucleic acid or amino acid “identity”. In certain embodiments, the length of a sequence aligned for comparison purposes is at least 30%, for example, at least 40%, in certain embodiments at least 60%, and in other embodiments at least 70%, 80%, 90% or 95% of the length of the reference sequence. The actual comparison of the two sequences can be accomplished by well-known methods, for example, using a mathematical algorithm. A preferred, non-limiting example of such a mathematical algorithm is described in Karlin *et al.*, *Proc. Natl. Acad. Sci. USA* 90:5873-5877 (1993). Such an algorithm is incorporated into the NBLAST and XBLAST programs (version 2.0) as described in Altschul *et al.*, *Nucleic Acids Res.* 25:389-3402 (1997). When utilizing BLAST and Gapped BLAST programs, the default parameters of the respective programs (*e.g.*, NBLAST) can be used. In one embodiment, parameters for sequence comparison can be set at score=100, wordlength=12, or can be varied (*e.g.*, W=5 or W=20).

Another preferred, non-limiting example of a mathematical algorithm utilized for the comparison of sequences is the algorithm of Myers and Miller, *CABIOS* 4(1): 11-17 (1988). Such an algorithm is incorporated into the ALIGN

program (version 2.0) which is part of the GCG sequence alignment software package (Accelrys, Cambridge, UK). When utilizing the ALIGN program for comparing amino acid sequences, a PAM120 weight residue table, a gap length penalty of 12, and a gap penalty of 4 can be used. Additional algorithms for  
5 sequence analysis are known in the art and include ADVANCE and ADAM as described in Torellis and Robotti, *Comput. Appl. Biosci.* 10:3-5 (1994); and FASTA described in Pearson and Lipman, *Proc. Natl. Acad. Sci. USA* 85:2444-8 (1988).

In another embodiment, the percent identity between two amino acid  
10 sequences can be accomplished using the GAP program in the GCG software package using either a BLOSUM63 matrix or a PAM250 matrix, and a gap weight of 12, 10, 8, 6, or 4 and a length weight of 2, 3, or 4. In yet another embodiment, the percent identity between two nucleic acid sequences can be accomplished using the GAP program in the GCG software package using a gap  
15 weight of 50 and a length weight of 3.

The present invention also provides isolated nucleic acid molecules that contain a fragment or portion that hybridizes under highly stringent conditions to a nucleic acid sequence comprising SEQ ID NO: 1 or 3 or the complement of  
20 SEQ ID NO: 1 or 3, and also provides isolated nucleic acid molecules that contain a fragment or portion that hybridizes under highly stringent conditions to a nucleic acid sequence encoding an amino acid sequence of the invention or polymorphic variant thereof. The nucleic acid fragments of the invention are at least about 15, for example, at least about 18, 20, 23 or 25 nucleotides, and can be 30, 40, 50, 100, 200 or more nucleotides in length. Longer fragments, for  
25 example, 30 or more nucleotides in length, encoding antigenic polypeptides described herein are particularly useful, such as for the generation of antibodies as described below.

#### *Probes and Primers*

30 In a related aspect, the nucleic acid fragments of the invention are used as probes or primers in assays such as those described herein. "Probes" or "primers" are oligonucleotides that hybridize in a base-specific manner to a

complementary strand of nucleic acid molecules. Such probes and primers include polypeptide nucleic acids, as described in Nielsen *et al.*, (*Science* 254:1497-1500 (1991)).

5 A probe or primer comprises a region of nucleic acid that hybridizes to at least about 15, for example about 20-25, and in certain embodiments about 40, 50 or 75, consecutive nucleotides of a nucleic acid of the invention, such as a nucleic acid comprising a contiguous nucleic acid sequence of SEQ ID NOs: 1 or 3 or the complement of SEQ ID Nos: 1 or 3, or a nucleic acid sequence encoding an amino acid sequence of SEQ ID NO: 2 or polymorphic variant  
10 thereof. In preferred embodiments, a probe or primer comprises 100 or fewer nucleotides, in certain embodiments, from 6 to 50 nucleotides, for example, from 12 to 30 nucleotides. In other embodiments, the probe or primer is at least 70% identical to the contiguous nucleic acid sequence or to the complement of the contiguous nucleotide sequence, for example, at least 80% identical, in  
15 certain embodiments at least 90% identical, and in other embodiments at least 95% identical, or even capable of selectively hybridizing to the contiguous nucleic acid sequence or to the complement of the contiguous nucleotide sequence. Often, the probe or primer further comprises a label, *e.g.*, radioisotope, fluorescent compound, enzyme, or enzyme co-factor.

20 The nucleic acid molecules of the invention such as those described above can be identified and isolated using standard molecular biology techniques and the sequence information provided herein. For example, nucleic acid molecules can be amplified and isolated using the polymerase chain reaction and synthetic oligonucleotide primers based on one or more of SEQ ID  
25 NOs: 1 or 3, or the complement thereof, or designed based on nucleotides based on sequences encoding one or more of the amino acid sequences provided herein. See generally *PCR Technology: Principles and Applications for DNA Amplification* (ed. H.A. Erlich, Freeman Press, NY, NY, 1992); *PCR Protocols: A Guide to Methods and Applications* (Eds. Innis *et al.*, Academic Press, San  
30 Diego, CA, 1990); Mattila *et al.*, *Nucl. Acids Res.* 19:4967 (1991); Eckert *et al.*, *PCR Methods and Applications* 1:17 (1991); PCR (eds. McPherson *et al.*, IRL Press, Oxford); and U.S. Patent 4,683,202. The nucleic acid molecules can be

amplified using cDNA, mRNA or genomic DNA as a template, cloned into an appropriate vector and characterized by DNA sequence analysis.

Other suitable amplification methods include the ligase chain reaction (LCR) (see Wu and Wallace, *Genomics* 4:560 (1989), Landegren *et al.*, *Science* 241:1077 (1988), transcription amplification (Kwoh *et al.*, *Proc. Natl. Acad. Sci. USA* 86:1173 (1989)), and self-sustained sequence replication (Guatelli *et al.*, *Proc. Nat. Acad. Sci. USA* 87:1874 (1990)) and nucleic acid based sequence amplification (NASBA). The latter two amplification methods involve isothermal reactions based on isothermal transcription, which produce both single stranded RNA (ssRNA) and double stranded DNA (dsDNA) as the amplification products in a ratio of about 30 or 100 to 1, respectively.

The amplified DNA can be labeled, for example, radiolabeled, and used as a probe for screening a cDNA library derived from human cells, mRNA in zap express, ZIPLOX or other suitable vector. Corresponding clones can be isolated, DNA can be obtained following *in vivo* excision, and the cloned insert can be sequenced in either or both orientations by art recognized methods to identify the correct reading frame encoding a polypeptide of the appropriate molecular weight. For example, the direct analysis of the nucleic acid molecules of the present invention can be accomplished using well-known methods that are commercially available. See, for example, Sambrook *et al.*, *Molecular Cloning, A Laboratory Manual* (2nd Ed., CSHP, New York 1989); Zyskind *et al.*, *Recombinant DNA Laboratory Manual*, (Acad. Press, 1988)). Using these or similar methods, the polypeptide and the DNA encoding the polypeptide can be isolated, sequenced and further characterized.

Antisense nucleic acid molecules of the invention can be designed using the nucleotide sequences of SEQ ID NOs: 1 or 3 and/or the complement of one or more of SEQ ID NOs: 1 or 3 and/or a portion of one or more of SEQ ID NOs: 1 or 3 or the complement of one or more of SEQ ID NOs: 1 or 3 and/or a sequence encoding the amino acid sequences of SEQ ID NOs: 2 or encoding a portion of one or more of SEQ ID NOs: 1 or 3 or their complement. They can be constructed using chemical synthesis and enzymatic ligation reactions using procedures known in the art. For example, an antisense nucleic acid molecule

(*e.g.*, an antisense oligonucleotide) can be chemically synthesized using naturally occurring nucleotides or variously modified nucleotides designed to increase the biological stability of the molecules or to increase the physical stability of the duplex formed between the antisense and sense nucleic acids, *e.g.*, phosphorothioate derivatives and acridine substituted nucleotides can be used. Alternatively, the antisense nucleic acid molecule can be produced biologically using an expression vector into which a nucleic acid molecule has been subcloned in an antisense orientation (*i.e.*, RNA transcribed from the inserted nucleic acid molecule will be of an antisense orientation to a target nucleic acid of interest).

The nucleic acid sequences can also be used to compare with endogenous DNA sequences in patients to identify one or more of the disorders related to FLAP, and as probes, such as to hybridize and discover related DNA sequences or to subtract out known sequences from a sample. The nucleic acid sequences can further be used to derive primers for genetic fingerprinting, to raise anti-polypeptide antibodies using DNA immunization techniques, and as an antigen to raise anti-DNA antibodies or elicit immune responses. Portions or fragments of the nucleotide sequences identified herein (and the corresponding complete gene sequences) can be used in numerous ways as polynucleotide reagents. For example, these sequences can be used to: (i) map their respective genes on a chromosome; and, thus, locate gene regions or nucleic acid regions associated with genetic disease; (ii) identify an individual from a minute biological sample (tissue typing); and (iii) aid in forensic identification of a biological sample. Additionally, the nucleotide sequences of the invention can be used to identify and express recombinant polypeptides for analysis, characterization or therapeutic use, or as markers for tissues in which the corresponding polypeptide is expressed, either constitutively, during tissue differentiation, or in diseased states. The nucleic acid sequences can additionally be used as reagents in the screening and/or diagnostic assays described herein, and can also be included as components of kits (*e.g.*, reagent kits) for use in the screening and/or diagnostic assays described herein.

*Vectors*

Another aspect of the invention pertains to nucleic acid constructs containing a nucleic acid molecule of SEQ ID NOs: 1 or 3 or the complement thereof (or a portion thereof). Yet another aspect of the invention pertains to  
5 nucleic acid constructs containing a nucleic acid molecule encoding an amino acid of SEQ ID NO: 2 or polymorphic variant thereof. The constructs comprise a vector (*e.g.*, an expression vector) into which a sequence of the invention has been inserted in a sense or antisense orientation. As used herein, the term “vector” refers to a nucleic acid molecule capable of transporting another  
10 nucleic acid to which it has been linked. One type of vector is a “plasmid”, which refers to a circular double stranded DNA loop into which additional DNA segments can be ligated. Another type of vector is a viral vector, wherein additional DNA segments can be ligated into the viral genome. Certain vectors are capable of autonomous replication in a host cell into which they are  
15 introduced (*e.g.*, bacterial vectors having a bacterial origin of replication and episomal mammalian vectors). Other vectors (*e.g.*, non-episomal mammalian vectors) are integrated into the genome of a host cell upon introduction into the host cell, and thereby are replicated along with the host genome. Moreover, certain vectors, such as expression vectors, are capable of directing the  
20 expression of genes or nucleic acids to which they are operably linked. In general, expression vectors of utility in recombinant DNA techniques are often in the form of plasmids. However, the invention is intended to include such other forms of expression vectors, such as viral vectors (*e.g.*, replication defective retroviruses, adenoviruses and adeno-associated viruses) that serve  
25 equivalent functions.

Preferred recombinant expression vectors of the invention comprise a nucleic acid molecule of the invention in a form suitable for expression of the nucleic acid molecule in a host cell. This means that the recombinant  
expression vectors include one or more regulatory sequences, selected on the  
30 basis of the host cells to be used for expression, which is operably linked to the nucleic acid sequence to be expressed. Within a recombinant expression vector, “operably linked” or “operatively linked” is intended to mean that the nucleic



acid sequence of interest is linked to the regulatory sequence(s) in a manner which allows for expression of the nucleic acid sequence (*e.g.*, in an *in vitro* transcription/translation system or in a host cell when the vector is introduced into the host cell). The term “regulatory sequence” is intended to include  
5 promoters, enhancers and other expression control elements (*e.g.*, polyadenylation signals). Such regulatory sequences are described, for example, in Goeddel, “Gene Expression Technology”, *Methods in Enzymology* 185, Academic Press, San Diego, CA (1990). Regulatory sequences include those which direct constitutive expression of a nucleic acid sequence in many  
10 types of host cell and those which direct expression of the nucleic acid sequence only in certain host cells (*e.g.*, tissue-specific regulatory sequences). It will be appreciated by those skilled in the art that the design of the expression vector can depend on such factors as the choice of the host cell to be transformed and the level of expression of polypeptide desired. The expression vectors of the  
15 invention can be introduced into host cells to thereby produce polypeptides, including fusion polypeptides, encoded by nucleic acid molecules as described herein.

The recombinant expression vectors of the invention can be designed for expression of a polypeptide of the invention in prokaryotic or eukaryotic cells,  
20 *e.g.*, bacterial cells such as *E. coli*, insect cells (using baculovirus expression vectors), yeast cells or mammalian cells. Suitable host cells are discussed further in Goeddel, *supra*. Alternatively, the recombinant expression vector can be transcribed and translated *in vitro*, for example using T7 promoter regulatory sequences and T7 polymerase.

25 Another aspect of the invention pertains to host cells into which a recombinant expression vector of the invention has been introduced. The terms “host cell” and “recombinant host cell” are used interchangeably herein. It is understood that such terms refer not only to the particular subject cell but also to the progeny or potential progeny of such a cell. Because certain modifications  
30 may occur in succeeding generations due to either mutation or environmental influences, such progeny may not, in fact, be identical to the parent cell, but are still included within the scope of the term as used herein.

5 A host cell can be any prokaryotic or eukaryotic cell. For example, a nucleic acid molecule of the invention can be expressed in bacterial cells (*e.g.*, *E. coli*), insect cells, yeast or mammalian cells (such as Chinese hamster ovary cells (CHO) or COS cells). Other suitable host cells are known to those skilled in the art.

10 Vector DNA can be introduced into prokaryotic or eukaryotic cells via conventional transformation or transfection techniques. As used herein, the terms “transformation” and “transfection” are intended to refer to a variety of art-recognized techniques for introducing a foreign nucleic acid molecule (*e.g.*, DNA) into a host cell, including calcium phosphate or calcium chloride co-precipitation, DEAE-dextran-mediated transfection, lipofection, or electroporation. Suitable methods for transforming or transfecting host cells can be found in Sambrook, *et al.* (*supra*), and other laboratory manuals.

15 For stable transfection of mammalian cells, it is known that, depending upon the expression vector and transfection technique used, only a small fraction of cells may integrate the foreign DNA into their genome. In order to identify and select these integrants, a gene or nucleic acid that encodes a selectable marker (*e.g.*, for resistance to antibiotics) is generally introduced into the host cells along with the gene or nucleic acid of interest. Preferred  
20 selectable markers include those that confer resistance to drugs, such as G418, hygromycin and methotrexate. Nucleic acid molecules encoding a selectable marker can be introduced into a host cell on the same vector as the nucleic acid molecule of the invention or can be introduced on a separate vector. Cells stably transfected with the introduced nucleic acid molecule can be identified by  
25 drug selection (*e.g.*, cells that have incorporated the selectable marker gene or nucleic acid will survive, while the other cells die).

30 A host cell of the invention, such as a prokaryotic host cell or eukaryotic host cell in culture can be used to produce (*i.e.*, express) a polypeptide of the invention. Accordingly, the invention further provides methods for producing a polypeptide using the host cells of the invention. In one embodiment, the method comprises culturing the host cell of invention (into which a recombinant expression vector encoding a polypeptide of the invention has been introduced)

in a suitable medium such that the polypeptide is produced. In another embodiment, the method further comprises isolating the polypeptide from the medium or the host cell.

5 The host cells of the invention can also be used to produce nonhuman transgenic animals. For example, in one embodiment, a host cell of the invention is a fertilized oocyte or an embryonic stem cell into which a nucleic acid molecule of the invention has been introduced (*e.g.*, an exogenous FLAP nucleic acid, or an exogenous nucleic acid encoding a FLAP polypeptide). Such host cells can then be used to create non-human transgenic animals in  
10 which exogenous nucleotide sequences have been introduced into the genome or homologous recombinant animals in which endogenous nucleotide sequences have been altered. Such animals are useful for studying the function and/or activity of the nucleic acid sequence and polypeptide encoded by the sequence and for identifying and/or evaluating modulators of their activity. As used  
15 herein, a “transgenic animal” is a non-human animal, preferably a mammal, more preferably a rodent such as a rat or mouse, in which one or more of the cells of the animal include a transgene. Other examples of transgenic animals include non-human primates, sheep, dogs, cows, goats, chickens and amphibians. A transgene is exogenous DNA which is integrated into the  
20 genome of a cell from which a transgenic animal develops and which remains in the genome of the mature animal, thereby directing the expression of an encoded gene product in one or more cell types or tissues of the transgenic animal. As used herein, a “homologous recombinant animal” is a non-human animal, preferably a mammal, more preferably a mouse, in which an  
25 endogenous gene has been altered by homologous recombination between the endogenous gene and an exogenous DNA molecule introduced into a cell of the animal, *e.g.*, an embryonic cell of the animal, prior to development of the animal.

30 Methods for generating transgenic animals via embryo manipulation and microinjection, particularly animals such as mice, have become conventional in the art and are described, for example, in U.S. Patent Nos. 4,736,866 and 4,870,009, U.S. Pat. No. 4,873,191 and in Hogan, *Manipulating the Mouse*

*Embryo* (Cold Spring Harbor Laboratory Press, Cold Spring Harbor, N.Y., 1986). Methods for constructing homologous recombination vectors and homologous recombinant animals are described further in Bradley, *Current Opinion in BioTechnology* 2:823-829 (1991) and in PCT Publication Nos. WO 90/11354, WO 91/01140, WO 92/0968, and WO 93/04169. Clones of the non-human transgenic animals described herein can also be produced according to the methods described in Wilmut *et al.*, *Nature* 385:810-813 (1997) and PCT Publication Nos. WO 97/07668 and WO 97/07669.

## POLYPEPTIDES OF THE INVENTION

The present invention also pertains to isolated polypeptides encoded by FLAP nucleic acids ("FLAP polypeptides"), and fragments and variants thereof, as well as polypeptides encoded by nucleotide sequences described herein (*e.g.*, other splicing variants). The term "polypeptide" refers to a polymer of amino acids, and not to a specific length; thus, peptides, oligopeptides and proteins are included within the definition of a polypeptide. As used herein, a polypeptide is said to be "isolated" or "purified" when it is substantially free of cellular material when it is isolated from recombinant and non-recombinant cells, or free of chemical precursors or other chemicals when it is chemically synthesized. A polypeptide, however, can be joined to another polypeptide with which it is not normally associated in a cell (*e.g.*, in a "fusion protein") and still be "isolated" or "purified."

The polypeptides of the invention can be purified to homogeneity. It is understood, however, that preparations in which the polypeptide is not purified to homogeneity are useful. The critical feature is that the preparation allows for the desired function of the polypeptide, even in the presence of considerable amounts of other components. Thus, the invention encompasses various degrees of purity. In one embodiment, the language "substantially free of cellular material" includes preparations of the polypeptide having less than about 30% (by dry weight) other proteins (*i.e.*, contaminating protein), less than about 20% other proteins, less than about 10% other proteins, or less than about 5% other proteins.

When a polypeptide is recombinantly produced, it can also be substantially free of culture medium, *i.e.*, culture medium represents less than about 20%, less than about 10%, or less than about 5% of the volume of the polypeptide preparation. The language “substantially free of chemical precursors or other chemicals” includes preparations of the polypeptide in which it is separated from chemical precursors or other chemicals that are involved in its synthesis. In one embodiment, the language “substantially free of chemical precursors or other chemicals” includes preparations of the polypeptide having less than about 30% (by dry weight) chemical precursors or other chemicals, less than about 20% chemical precursors or other chemicals, less than about 10% chemical precursors or other chemicals, or less than about 5% chemical precursors or other chemicals.

In one embodiment, a polypeptide of the invention comprises an amino acid sequence encoded by a nucleic acid molecule comprising a nucleic acid sequence selected from the group consisting of SEQ ID NO: 1 or 3, or the complement of SEQ ID NO: 1 or 3, or portions thereof, or a portion or polymorphic variant thereof. However, the polypeptides of the invention also encompass fragment and sequence variants. Variants include a substantially homologous polypeptide encoded by the same genetic locus in an organism, *i.e.*, an allelic variant, as well as other splicing variants. Variants also encompass polypeptides derived from other genetic loci in an organism, but having substantial homology to a polypeptide encoded by a nucleic acid molecule comprising a nucleic acid sequence selected from the group consisting of SEQ ID NOs: 1 or 3 or their complement, or portions thereof, or having substantial homology to a polypeptide encoded by a nucleic acid molecule comprising a nucleic acid sequence selected from the group consisting of nucleotide sequences encoding SEQ ID NO: 2 or polymorphic variants thereof. Variants also include polypeptides substantially homologous or identical to these polypeptides but derived from another organism, *i.e.*, an ortholog. Variants also include polypeptides that are substantially homologous or identical to these polypeptides that are produced by chemical synthesis. Variants also include

polypeptides that are substantially homologous or identical to these polypeptides that are produced by recombinant methods.

As used herein, two polypeptides (or a region of the polypeptides) are substantially homologous or identical when the amino acid sequences are at least about 45-55%, in certain embodiments at least about 70-75%, and in other  
5       embodiments at least about 80-85%, and in others greater than about 90% or more homologous or identical. A substantially homologous amino acid sequence, according to the present invention, will be encoded by a nucleic acid molecule hybridizing to SEQ ID NO: 1 or 3 or portion thereof, under stringent  
10       conditions as more particularly described above, or will be encoded by a nucleic acid molecule hybridizing to a nucleic acid sequence encoding SEQ ID NO: 2 or a portion thereof or polymorphic variant thereof, under stringent conditions as more particularly described thereof.

The invention also encompasses polypeptides having a lower degree of identity but having sufficient similarity so as to perform one or more of the  
15       same functions performed by a polypeptide encoded by a nucleic acid molecule of the invention. Similarity is determined by conserved amino acid substitution. Such substitutions are those that substitute a given amino acid in a polypeptide by another amino acid of like characteristics. Conservative substitutions are  
20       likely to be phenotypically silent. Typically seen as conservative substitutions are the replacements, one for another, among the aliphatic amino acids Ala, Val, Leu and Ile; interchange of the hydroxyl residues Ser and Thr, exchange of the acidic residues Asp and Glu, substitution between the amide residues Asn and Gln, exchange of the basic residues Lys and Arg and replacements among the  
25       aromatic residues Phe and Tyr. Guidance concerning which amino acid changes are likely to be phenotypically silent are found in Bowie *et al.*, *Science* 247:1306-1310 (1990).

A variant polypeptide can differ in amino acid sequence by one or more substitutions, deletions, insertions, inversions, fusions, and truncations or a  
30       combination of any of these. Further, variant polypeptides can be fully functional or can lack function in one or more activities. Fully functional variants typically contain only conservative variation or variation in non-critical

residues or in non-critical regions. Functional variants can also contain substitution of similar amino acids that result in no change or an insignificant change in function. Alternatively, such substitutions may positively or negatively affect function to some degree. Non-functional variants typically contain one or more non-conservative amino acid substitutions, deletions, insertions, inversions, or truncation or a substitution, insertion, inversion, or deletion in a critical residue or critical region.

Amino acids that are essential for function can be identified by methods known in the art, such as site-directed mutagenesis or alanine-scanning mutagenesis (Cunningham *et al.*, *Science* 244:1081-1085 (1989)). The latter procedure introduces single alanine mutations at every residue in the molecule. The resulting mutant molecules are then tested for biological activity *in vitro*, or *in vitro* proliferative activity. Sites that are critical for polypeptide activity can also be determined by structural analysis such as crystallization, nuclear magnetic resonance or photoaffinity labeling (Smith *et al.*, *J. Mol. Biol.* 224:899-904 (1992); de Vos *et al.*, *Science* 255:306-312 (1992)).

The invention also includes fragments of the polypeptides of the invention. Fragments can be derived from a polypeptide encoded by a nucleic acid molecule comprising SEQ ID NO: 1 or 3, or the complement of SEQ ID NO: 1 or 3 (or other variants). However, the invention also encompasses fragments of the variants of the polypeptides described herein. As used herein, a fragment comprises at least 6 contiguous amino acids. Useful fragments include those that retain one or more of the biological activities of the polypeptide as well as fragments that can be used as an immunogen to generate polypeptide-specific antibodies.

Biologically active fragments (peptides which are, for example, 6, 9, 12, 15, 16, 20, 30, 35, 36, 37, 38, 39, 40, 50, 100 or more amino acids in length) can comprise a domain, segment, or motif that has been identified by analysis of the polypeptide sequence using well-known methods, *e.g.*, signal peptides, extracellular domains, one or more transmembrane segments or loops, ligand binding regions, zinc finger domains, DNA binding domains, acylation sites, glycosylation sites, or phosphorylation sites.

Fragments can be discrete (not fused to other amino acids or polypeptides) or can be within a larger polypeptide. Further, several fragments can be comprised within a single larger polypeptide. In one embodiment a fragment designed for expression in a host can have heterologous pre- and pro-polypeptide regions fused to the amino terminus of the polypeptide fragment and an additional region fused to the carboxyl terminus of the fragment.

The invention thus provides chimeric or fusion polypeptides. These comprise a polypeptide of the invention operatively linked to a heterologous protein or polypeptide having an amino acid sequence not substantially homologous to the polypeptide. "Operatively linked" indicates that the polypeptide and the heterologous protein are fused in-frame. The heterologous protein can be fused to the N-terminus or C-terminus of the polypeptide. In one embodiment the fusion polypeptide does not affect function of the polypeptide *per se*. For example, the fusion polypeptide can be a GST-fusion polypeptide in which the polypeptide sequences are fused to the C-terminus of the GST sequences. Other types of fusion polypeptides include, but are not limited to, enzymatic fusion polypeptides, for example beta-galactosidase fusions, yeast two-hybrid GAL fusions, poly-His fusions and Ig fusions. Such fusion polypeptides, particularly poly-His fusions, can facilitate the purification of recombinant polypeptide. In certain host cells (*e.g.*, mammalian host cells), expression and/or secretion of a polypeptide can be increased using a heterologous signal sequence. Therefore, in another embodiment, the fusion polypeptide contains a heterologous signal sequence at its N-terminus.

EP-A-O 464 533 discloses fusion proteins comprising various portions of immunoglobulin constant regions. The Fc is useful in therapy and diagnosis and thus results, for example, in improved pharmacokinetic properties (EP-A 0232 262). In drug discovery, for example, human proteins have been fused with Fc portions for the purpose of high-throughput screening assays to identify antagonists. Bennett *et al.*, *Journal of Molecular Recognition*, 8:52-58 (1995) and Johanson *et al.*, *The Journal of Biological Chemistry*, 270, 16:9459-9471 (1995). Thus, this invention also encompasses soluble fusion polypeptides containing a polypeptide of the invention and various portions of the constant



regions of heavy or light chains of immunoglobulins of various subclasses (IgG, IgM, IgA, IgE).

A chimeric or fusion polypeptide can be produced by standard recombinant DNA techniques. For example, DNA fragments coding for the  
5 different polypeptide sequences are ligated together in-frame in accordance with conventional techniques. In another embodiment, the fusion gene can be synthesized by conventional techniques including automated DNA synthesizers. Alternatively, PCR amplification of nucleic acid fragments can be carried out using anchor primers which give rise to complementary overhangs between two  
10 consecutive nucleic acid fragments which can subsequently be annealed and re-amplified to generate a chimeric nucleic acid sequence (see Ausubel *et al.*, *Current Protocols in Molecular Biology*, 1992). Moreover, many expression vectors are commercially available that already encode a fusion moiety (*e.g.*, a GST protein). A nucleic acid molecule encoding a polypeptide of the invention  
15 can be cloned into such an expression vector such that the fusion moiety is linked in-frame to the polypeptide.

The isolated polypeptide can be purified from cells that naturally express it, purified from cells that have been altered to express it (recombinant), or synthesized using known protein synthesis methods. In one embodiment, the  
20 polypeptide is produced by recombinant DNA techniques. For example, a nucleic acid molecule encoding the polypeptide is cloned into an expression vector, the expression vector introduced into a host cell and the polypeptide expressed in the host cell. The polypeptide can then be isolated from the cells by an appropriate purification scheme using standard protein purification  
25 techniques.

The polypeptides of the present invention can be used to raise antibodies or to elicit an immune response. The polypeptides can also be used as a reagent, *e.g.*, a labeled reagent, in assays to quantitatively determine levels of the polypeptide or a molecule to which it binds (*e.g.*, a ligand) in biological  
30 fluids. The polypeptides can also be used as markers for cells or tissues in which the corresponding polypeptide is preferentially expressed, either constitutively, during tissue differentiation, or in diseased states. The

polypeptides can be used to isolate a corresponding binding agent, *e.g.*, ligand, such as, for example, in an interaction trap assay, and to screen for peptide or small molecule antagonists or agonists of the binding interaction. For example, because members of the leukotriene pathway including FLAP bind to receptors, the leukotriene pathway polypeptides can be used to isolate such receptors.

#### ANTIBODIES OF THE INVENTION

Polyclonal and/or monoclonal antibodies that specifically bind one form of the polypeptide or nucleic acid product (*e.g.*, a polypeptide encoded by a nucleic acid having a SNP as set forth in Table 13), but not to another form of the polypeptide or nucleic acid product, are also provided. Antibodies are also provided which bind a portion of either polypeptide encoded by nucleic acids of the invention (*e.g.*, SEQ ID NO: 1 or SEQ ID NO: 3, or the complement of SEQ ID NO: 1 or SEQ ID NO: 3), or to a polypeptide encoded by nucleic acids of the invention that contain a polymorphic site or sites. The invention also provides antibodies to the polypeptides and polypeptide fragments of the invention, or a portion thereof, or having an amino acid sequence encoded by a nucleic acid molecule comprising all or a portion of SEQ ID NOs: 1 or 3, or the complement thereof, or another variant or portion thereof.

The term “antibody” as used herein refers to immunoglobulin molecules and immunologically active portions of immunoglobulin molecules, *i.e.*, molecules that contain an antigen binding site that specifically binds an antigen. A molecule that specifically binds to a polypeptide of the invention is a molecule that binds to that polypeptide or a fragment thereof, but does not substantially bind other molecules in a sample, *e.g.*, a biological sample, which naturally contains the polypeptide. Examples of immunologically active portions of immunoglobulin molecules include F(ab) and F(ab')<sub>2</sub> fragments which can be generated by treating the antibody with an enzyme such as pepsin. The invention provides polyclonal and monoclonal antibodies that bind to a polypeptide of the invention. The term “monoclonal antibody” or “monoclonal antibody composition”, as used herein, refers to a population of antibody molecules that contain only one species of an antigen binding site capable of

immunoreacting with a particular epitope of a polypeptide of the invention. A monoclonal antibody composition thus typically displays a single binding affinity for a particular polypeptide of the invention with which it immunoreacts.

5            Polyclonal antibodies can be prepared as described above by immunizing a suitable subject with a desired immunogen, *e.g.*, polypeptide of the invention or fragment thereof. The antibody titer in the immunized subject can be monitored over time by standard techniques, such as with an enzyme linked immunosorbent assay (ELISA) using immobilized polypeptide. If  
10           desired, the antibody molecules directed against the polypeptide can be isolated from the mammal (*e.g.*, from the blood) and further purified by well-known techniques, such as protein A chromatography to obtain the IgG fraction. At an appropriate time after immunization, *e.g.*, when the antibody titers are highest, antibody-producing cells can be obtained from the subject and used to prepare  
15           monoclonal antibodies by standard techniques, such as the hybridoma technique originally described by Kohler and Milstein, *Nature* 256:495-497 (1975), the human B cell hybridoma technique (Kozbor *et al.*, *Immunol. Today* 4:72 (1983)); the EBV-hybridoma technique (Cole *et al.*, *Monoclonal Antibodies and Cancer Therapy*, Alan R. Liss, 1985, Inc., pp. 77-96); or trioma techniques.  
20           The technology for producing hybridomas is well known (see generally *Current Protocols in Immunology* (1994) Coligan *et al.* (eds.) John Wiley & Sons, Inc., New York, NY). Briefly, an immortal cell line (typically a myeloma) is fused to lymphocytes (typically splenocytes) from a mammal immunized with an immunogen as described above, and the culture supernatants of the resulting  
25           hybridoma cells are screened to identify a hybridoma producing a monoclonal antibody that binds a polypeptide of the invention.

             Any of the many well known protocols used for fusing lymphocytes and immortalized cell lines can be applied for the purpose of generating a monoclonal antibody to a polypeptide of the invention (see, *e.g.*, *Current*  
30           *Protocols in Immunology*, *supra*; Galfre *et al.*, *Nature* 266:55052 (1977); R.H. Kenneth, in *Monoclonal Antibodies: A New Dimension In Biological Analyses*, Plenum Publishing Corp., New York, New York (1980); and Lerner, *Yale J.*

*Biol. Med.* 54:387-402 (1981). Moreover, the ordinarily skilled worker will appreciate that there are many variations of such methods that also would be useful.

5 Alternative to preparing monoclonal antibody-secreting hybridomas, a monoclonal antibody to a polypeptide of the invention can be identified and isolated by screening a recombinant combinatorial immunoglobulin library (e.g., an antibody phage display library) with the polypeptide to thereby isolate immunoglobulin library members that bind the polypeptide. Kits for generating and screening phage display libraries are commercially available (e.g., the  
10 Pharmacia *Recombinant Phage Antibody System*, Catalog No. 27-9400-01; and the Stratagene *SurfZAP™* Phage Display Kit, Catalog No. 240612). Additionally, examples of methods and reagents particularly amenable for use in generating and screening antibody display library can be found in, for example, U.S. Patent No. 5,223,409; PCT Publication No. WO 92/18619; PCT  
15 Publication No. WO 91/17271; PCT Publication No. WO 92/20791; PCT Publication No. WO 92/15679; PCT Publication No. WO 93/01288; PCT Publication No. WO 92/01047; PCT Publication No. WO 92/09690; PCT Publication No. WO 90/02809; Fuchs *et al.*, *Bio/Technology* 9: 1370-1372 (1991); Hay *et al.*, *Hum. Antibod. Hybridomas* 3:81-85 (1992); Huse *et al.*,  
20 *Science* 246:1275-1281 (1989); Griffiths *et al.*, *EMBO J.* 12:725-734 (1993).

25 Additionally, recombinant antibodies, such as chimeric and humanized monoclonal antibodies, comprising both human and non-human portions, which can be made using standard recombinant DNA techniques, are within the scope of the invention. Such chimeric and humanized monoclonal antibodies can be produced by recombinant DNA techniques known in the art.

In general, antibodies of the invention (e.g., a monoclonal antibody) can be used to isolate a polypeptide of the invention by standard techniques, such as affinity chromatography or immunoprecipitation. A polypeptide-specific antibody can facilitate the purification of natural polypeptide from cells and of  
30 recombinantly produced polypeptide expressed in host cells. Moreover, an antibody specific for a polypeptide of the invention can be used to detect the polypeptide (e.g., in a cellular lysate, cell supernatant, or tissue sample) in order

to evaluate the abundance and pattern of expression of the polypeptide.

Antibodies can be used diagnostically to monitor protein levels in tissue as part of a clinical testing procedure, *e.g.*, to, for example, determine the efficacy of a given treatment regimen. Detection can be facilitated by coupling the antibody to a detectable substance. Examples of detectable substances include various enzymes, prosthetic groups, fluorescent materials, luminescent materials, bioluminescent materials, and radioactive materials. Examples of suitable enzymes include horseradish peroxidase, alkaline phosphatase,  $\beta$ -galactosidase, or acetylcholinesterase; examples of suitable prosthetic group complexes include streptavidin/biotin and avidin/biotin; examples of suitable fluorescent materials include umbelliferone, fluorescein, fluorescein isothiocyanate, rhodamine, dichlorotriazinylamine fluorescein, dansyl chloride or phycoerythrin; an example of a luminescent material includes luminol; examples of bioluminescent materials include luciferase, luciferin and aequorin, and examples of suitable radioactive material include  $^{125}\text{I}$ ,  $^{131}\text{I}$ ,  $^{35}\text{S}$  or  $^3\text{H}$ .

As described above, antibodies to leukotrienes can be used in the methods of the invention. The methods described herein can be used to generate such antibodies for use in the methods.

## DIAGNOSTIC ASSAYS

The nucleic acids, probes, primers, polypeptides and antibodies described herein can be used in methods of diagnosis of a susceptibility to MI, ACS, stroke or PAOD, or to another disease or condition associated with an MI gene, such as FLAP, as well as in kits useful for diagnosis of a susceptibility to MI, ACS, stroke or PAOD, or to another disease or condition associated with FLAP. In one embodiment, the kit useful for diagnosis of susceptibility to MI, ACS, stroke or PAOD, or to another disease or condition associated with FLAP comprises primers as described herein, wherein the primers contain one or more of the SNPs identified in Table 13.

In one embodiment of the invention, diagnosis of susceptibility to MI, ACS, stroke or PAOD (or diagnosis of susceptibility to another disease or condition associated with FLAP), is made by detecting a polymorphism in a

FLAP nucleic acid as described herein. The polymorphism can be an alteration in a FLAP nucleic acid, such as the insertion or deletion of a single nucleotide, or of more than one nucleotide, resulting in a frame shift alteration; the change of at least one nucleotide, resulting in a change in the encoded amino acid; the change of at least one nucleotide, resulting in the generation of a premature stop codon; the deletion of several nucleotides, resulting in a deletion of one or more amino acids encoded by the nucleotides; the insertion of one or several nucleotides, such as by unequal recombination or gene conversion, resulting in an interruption of the coding sequence of the gene or nucleic acid; duplication of all or a part of the gene or nucleic acid; transposition of all or a part of the gene or nucleic acid; or rearrangement of all or a part of the gene or nucleic acid. More than one such alteration may be present in a single gene or nucleic acid. Such sequence changes cause an alteration in the polypeptide encoded by a FLAP nucleic acid. For example, if the alteration is a frame shift alteration, the frame shift can result in a change in the encoded amino acids, and/or can result in the generation of a premature stop codon, causing generation of a truncated polypeptide. Alternatively, a polymorphism associated with a disease or condition associated with a FLAP nucleic acid or a susceptibility to a disease or condition associated with a FLAP nucleic acid can be a synonymous alteration in one or more nucleotides (*i.e.*, an alteration that does not result in a change in the polypeptide encoded by a FLAP nucleic acid). Such a polymorphism may alter splicing sites, affect the stability or transport of mRNA, or otherwise affect the transcription or translation of the nucleic acid. A FLAP nucleic acid that has any of the alteration described above is referred to herein as an "altered nucleic acid."

In a first method of diagnosing a susceptibility to MI, ACS, stroke or PAOD, hybridization methods, such as Southern analysis, Northern analysis, or *in situ* hybridizations, can be used (see *Current Protocols in Molecular Biology*, Ausubel, F. *et al.*, eds., John Wiley & Sons, including all supplements through 1999). For example, a biological sample from a test subject (a "test sample") of genomic DNA, RNA, or cDNA, is obtained from an individual suspected of having, being susceptible to or predisposed for, or carrying a defect for, a

susceptibility to a disease or condition associated with a FLAP nucleic acid (the “test individual”). The individual can be an adult, child, or fetus. The test sample can be from any source which contains genomic DNA, such as a blood sample, sample of amniotic fluid, sample of cerebrospinal fluid, or tissue sample from skin, muscle, buccal or conjunctival mucosa, placenta, gastrointestinal tract or other organs. A test sample of DNA from fetal cells or tissue can be obtained by appropriate methods, such as by amniocentesis or chorionic villus sampling. The DNA, RNA, or cDNA sample is then examined to determine whether a polymorphism in an MI nucleic acid is present, and/or to determine which splicing variant(s) encoded by the FLAP is present. The presence of the polymorphism or splicing variant(s) can be indicated by hybridization of the nucleic acid in the genomic DNA, RNA, or cDNA to a nucleic acid probe. A “nucleic acid probe,” as used herein, can be a DNA probe or an RNA probe; the nucleic acid probe can contain at least one polymorphism in a FLAP nucleic acid or contains a nucleic acid encoding a particular splicing variant of a FLAP nucleic acid. The probe can be any of the nucleic acid molecules described above (e.g., the nucleic acid, a fragment, a vector comprising the nucleic acid, a probe or primer, etc.).

To diagnose a susceptibility to MI, ACS, stroke or PAOD (or another disease or condition associated with FLAP), the test sample containing a FLAP nucleic acid is contacted with at least one nucleic acid probe to form a hybridization sample. A preferred probe for detecting mRNA or genomic DNA is a labeled nucleic acid probe capable of hybridizing to mRNA or genomic DNA sequences described herein. The nucleic acid probe can be, for example, a full-length nucleic acid molecule, or a portion thereof, such as an oligonucleotide of at least 15, 30, 50, 100, 250 or 500 nucleotides in length and sufficient to specifically hybridize under stringent conditions to appropriate mRNA or genomic DNA. For example, the nucleic acid probe can be all or a portion of one of SEQ ID NOs: 1 and 3, or the complement thereof or a portion thereof; or can be a nucleic acid encoding all or a portion of one of SEQ ID NO: 2. Other suitable probes for use in the diagnostic assays of the invention are

described above (see *e.g.*, probes and primers discussed under the heading, “Nucleic Acids of the Invention”).

The hybridization sample is maintained under conditions that are sufficient to allow specific hybridization of the nucleic acid probe to a FLAP nucleic acid. “Specific hybridization,” as used herein, indicates exact  
5 hybridization (*e.g.*, with no mismatches). Specific hybridization can be performed under high stringency conditions or moderate stringency conditions, for example, as described above. In a particularly preferred embodiment, the hybridization conditions for specific hybridization are high stringency.

Specific hybridization, if present, is then detected using standard  
10 methods. If specific hybridization occurs between the nucleic acid probe and FLAP nucleic acid in the test sample, then the FLAP has the polymorphism, or is the splicing variant, that is present in the nucleic acid probe. More than one nucleic acid probe can also be used concurrently in this method. Specific  
15 hybridization of any one of the nucleic acid probes is indicative of a polymorphism in the FLAP nucleic acid, or of the presence of a particular splicing variant encoding the FLAP nucleic acid, and is therefore diagnostic for a susceptibility to a disease or condition associated with FLAP (*e.g.*, MI, ACS, stroke or PAOD).

In Northern analysis (see *Current Protocols in Molecular Biology*, Ausubel, F. *et al.*, eds., John Wiley & Sons, *supra*) the hybridization methods described above are used to identify the presence of a polymorphism or a particular splicing variant, associated with a susceptibility to a disease or condition associated with FLAP (*e.g.*, MI, ACS, stroke or PAOD). For  
20 Northern analysis, a test sample of RNA is obtained from the individual by appropriate means. Specific hybridization of a nucleic acid probe, as described above, to RNA from the individual is indicative of a polymorphism in a FLAP nucleic acid, or of the presence of a particular splicing variant encoded by a FLAP nucleic acid, and is therefore diagnostic for susceptibility to a disease or  
25 condition associated with FLAP (*e.g.*, MI, ACS, stroke or PAOD).  
30

For representative examples of use of nucleic acid probes, see, for example, U.S. Patents No. 5,288,611 and 4,851,330.



Alternatively, a peptide nucleic acid (PNA) probe can be used instead of a nucleic acid probe in the hybridization methods described above. PNA is a DNA mimic having a peptide-like, inorganic backbone, such as N-(2-aminoethyl)glycine units, with an organic base (A, G, C, T or U) attached to the glycine nitrogen via a methylene carbonyl linker (see, for example, Nielsen, P.E. *et al.*, *Bioconjugate Chemistry* 5, American Chemical Society, p. 1 (1994)). The PNA probe can be designed to specifically hybridize to a nucleic acid having a polymorphism associated with a susceptibility to a disease or condition associated with FLAP (*e.g.*, MI). Hybridization of the PNA probe to a FLAP nucleic acid as described herein is diagnostic for the susceptibility to the disease or condition.

In another method of the invention, mutation analysis by restriction digestion can be used to detect an altered nucleic acid, or nucleic acids containing a polymorphism(s), if the mutation or polymorphism in the nucleic acid results in the creation or elimination of a restriction site. A test sample containing genomic DNA is obtained from the individual. Polymerase chain reaction (PCR) can be used to amplify a FLAP nucleic acid (and, if necessary, the flanking sequences) in the test sample of genomic DNA from the test individual. RFLP analysis is conducted as described (see *Current Protocols in Molecular Biology, supra*). The digestion pattern of the relevant DNA fragment indicates the presence or absence of the alteration or polymorphism in the FLAP nucleic acid, and therefore indicates the presence or absence of the susceptibility to a disease or condition associated with FLAP (*e.g.*, MI, ACS, stroke or PAOD).

Sequence analysis can also be used to detect specific polymorphisms in the FLAP nucleic acid. A test sample of DNA or RNA is obtained from the test individual. PCR or other appropriate methods can be used to amplify the nucleic acid, and/or its flanking sequences, if desired. The sequence of a FLAP nucleic acid, or a fragment of the nucleic acid, or cDNA, or fragment of the cDNA, or mRNA, or fragment of the mRNA, is determined, using standard methods. The sequence of the nucleic acid, nucleic acid fragment, cDNA, cDNA fragment, mRNA, or mRNA fragment is compared with the known

nucleic acid sequence of the nucleic acid, cDNA (*e.g.*, one or more of SEQ ID NOs: 1 or 3, and/or the complement of SEQ ID NO: 1 or 3), or a nucleic acid sequence encoding SEQ ID NO: 2 or a fragment thereof) or mRNA, as appropriate. The presence of a polymorphism in the FLAP indicates that the individual has a susceptibility to a disease associated with FLAP (*e.g.*, MI, ACS, stroke or PAOD).

Allele-specific oligonucleotides can also be used to detect the presence of polymorphism(s) in the FLAP nucleic acid, through the use of dot-blot hybridization of amplified oligonucleotides with allele-specific oligonucleotide (ASO) probes (see, for example, Saiki, R. *et al.*, *Nature* 324:163-166 (1986)). An "allele-specific oligonucleotide" (also referred to herein as an "allele-specific oligonucleotide probe") is an oligonucleotide of approximately 10-50 base pairs, for example, approximately 15-30 base pairs, that specifically hybridizes to a FLAP nucleic acid, and that contains a polymorphism associated with a susceptibility to a disease or condition associated with FLAP (*e.g.*, MI, ACS, stroke or PAOD). An allele-specific oligonucleotide probe that is specific for particular polymorphisms in a FLAP nucleic acid can be prepared, using standard methods (see *Current Protocols in Molecular Biology, supra*). To identify polymorphisms in the nucleic acid associated with susceptibility to disease, a test sample of DNA is obtained from the individual. PCR can be used to amplify all or a fragment of a FLAP nucleic acid, and its flanking sequences. The DNA containing the amplified FLAP nucleic acid (or fragment of the nucleic acid) is dot-blotted, using standard methods (see *Current Protocols in Molecular Biology, supra*), and the blot is contacted with the oligonucleotide probe. The presence of specific hybridization of the probe to the amplified FLAP is then detected. Specific hybridization of an allele-specific oligonucleotide probe to DNA from the individual is indicative of a polymorphism in the FLAP, and is therefore indicative of a susceptibility to a disease or condition associated with FLAP (*e.g.*, MI, ACS, stroke or PAOD).

An allele-specific primer hybridizes to a site on target DNA overlapping a polymorphism and only primes amplification of an allelic form to which the primer exhibits perfect complementarity. See Gibbs, *Nucleic Acid Res.* 17,

2427-2448 (1989). This primer is used in conjunction with a second primer which hybridizes at a distal site. Amplification proceeds from the two primers, resulting in a detectable product which indicates the particular allelic form is present. A control is usually performed with a second pair of primers, one of which shows a single base mismatch at the polymorphic site and the other of which exhibits perfect complementarity to a distal site. The single-base mismatch prevents amplification and no detectable product is formed. The method works best when the mismatch is included in the 3'-most position of the oligonucleotide aligned with the polymorphism because this position is most destabilizing to elongation from the primer (see, *e.g.*, WO 93/22456).

With the addition of such analogs as locked nucleic acids (LNAs), the size of primers and probes can be reduced to as few as 8 bases. LNAs are a novel class of bicyclic DNA analogs in which the 2' and 4' positions in the furanose ring are joined via an O-methylene (oxy-LNA), S-methylene (thio-LNA), or amino methylene (amino-LNA) moiety. Common to all of these LNA variants is an affinity toward complementary nucleic acids, which is by far the highest reported for a DNA analog. For example, particular all oxy-LNA nonamers have been shown to have melting temperatures of 64°C and 74°C when in complex with complementary DNA or RNA, respectively, as opposed to 28°C for both DNA and RNA for the corresponding DNA nonamer. Substantial increases in  $T_m$  are also obtained when LNA monomers are used in combination with standard DNA or RNA monomers. For primers and probes, depending on where the LNA monomers are included (*e.g.*, the 3' end, the 5' end, or in the middle), the  $T_m$  could be increased considerably.

In another embodiment, arrays of oligonucleotide probes that are complementary to target nucleic acid sequence segments from an individual, can be used to identify polymorphisms in a FLAP nucleic acid. For example, in one embodiment, an oligonucleotide array can be used. Oligonucleotide arrays typically comprise a plurality of different oligonucleotide probes that are coupled to a surface of a substrate in different known locations. These oligonucleotide arrays, also described as "Genechips™," have been generally described in the art, for example, U.S. Pat. No. 5,143,854 and PCT patent

publication Nos. WO 90/15070 and WO 92/10092. These arrays can generally be produced using mechanical synthesis methods or light directed synthesis methods that incorporate a combination of photolithographic methods and solid phase oligonucleotide synthesis methods. See Fodor *et al.*, *Science* 251:767-777 (1991); Pirrung *et al.*, U.S. Pat. 5,143,854; (see also PCT Application WO 90/15070); Fodor *et al.*, PCT Publication WO 92/10092; and U.S. Pat. 5,424,186, the entire teachings of each of which are incorporated by reference herein. Techniques for the synthesis of these arrays using mechanical synthesis methods are described in, *e.g.*, U.S. Pat. 5,384,261, the entire teachings of which are incorporated by reference herein. In another example, linear arrays can be utilized.

Once an oligonucleotide array is prepared, a nucleic acid of interest is hybridized with the array and scanned for polymorphisms. Hybridization and scanning are generally carried out by methods described herein and also in, *e.g.*, published PCT Application Nos. WO 92/10092 and WO 95/11995, and U.S. Pat. No. 5,424,186, the entire teachings of which are incorporated by reference herein. In brief, a target nucleic acid sequence that includes one or more previously identified polymorphic markers is amplified using well-known amplification techniques, *e.g.*, PCR. Typically, this involves the use of primer sequences that are complementary to the two strands of the target sequence both upstream and downstream from the polymorphism. Asymmetric PCR techniques may also be used. Amplified target, generally incorporating a label, is then hybridized with the array under appropriate conditions. Upon completion of hybridization and washing of the array, the array is scanned to determine the position on the array to which the target sequence hybridizes. The hybridization data obtained from the scan is typically in the form of fluorescence intensities as a function of location on the array. In a reverse method, a probe, containing a polymorphism, can be coupled to a solid surface and PCR amplicons are then added to hybridize to these probes.

Although primarily described in terms of a single detection block, *e.g.*, detection of a single polymorphism arrays can include multiple detection blocks, and thus be capable of analyzing multiple, specific polymorphisms. It

will generally be understood that detection blocks may be grouped within a single array or in multiple, separate arrays so that varying, optimal conditions may be used during the hybridization of the target to the array. For example, it may often be desirable to provide for the detection of those polymorphisms that  
5 fall within G-C rich stretches of a genomic sequence, separately from those falling in A-T rich segments. This allows for the separate optimization of hybridization conditions for each situation.

Additional uses of oligonucleotide arrays for detection of polymorphisms can be found, for example, in U.S. Patents Nos. 5,858,659 and  
10 5,837,832, the entire teachings of which are incorporated by reference herein. Other methods of nucleic acid analysis can be used to detect polymorphisms in a nucleic acid described herein, or variants encoded by a nucleic acid described herein. Representative methods include direct manual sequencing (Church and Gilbert, *Proc. Natl. Acad. Sci. USA* 81:1991-1995 (1988); Sanger, F. *et al.*,  
15 *Proc. Natl. Acad. Sci., USA* 74:5463-5467 (1977); Beavis *et al.* U.S. Pat. No. 5,288,644); automated fluorescent sequencing; single-stranded conformation polymorphism assays (SSCP); clamped denaturing gel electrophoresis (CDGE); denaturing gradient gel electrophoresis (DGGE) (Sheffield, V.C. *et al.*, *Proc. Natl. Acad. Sci. USA* 86:232-236 (1989)), mobility shift analysis (Orita, M. *et al.*, *Proc. Natl. Acad. Sci. USA* 86:2766-2770 (1989)), restriction enzyme  
20 analysis (Flavell *et al.*, *Cell* 15:25 (1978); Geever, *et al.*, *Proc. Natl. Acad. Sci. USA* 78:5081 (1981)); heteroduplex analysis; chemical mismatch cleavage (CMC) (Cotton *et al.*, *Proc. Natl. Acad. Sci. USA* 85:4397-4401 (1985)); RNase protection assays (Myers, R.M. *et al.*, *Science* 230:1242 (1985)); use of  
25 polypeptides which recognize nucleotide mismatches, such as *E. coli* mutS protein; allele-specific PCR, for example.

In one embodiment of the invention, diagnosis of a susceptibility to a disease or condition associated with FLAP (*e.g.*, MI, ACS, stroke or PAOD) can also be made by expression analysis by quantitative PCR (kinetic thermal  
30 cycling). This technique utilizing TaqMan<sup>®</sup> can be used to allow the identification of polymorphisms and whether a patient is homozygous or heterozygous. The technique can assess the presence of an alteration in the

expression or composition of the polypeptide encoded by a FLAP nucleic acid or splicing variants encoded by a FLAP nucleic acid. Further, the expression of the variants can be quantified as physically or functionally different.

5 In another embodiment of the invention, diagnosis of a susceptibility to MI, ACS, stroke or PAOD (or of another disease or condition associated with FLAP) can also be made by examining expression and/or composition of a FLAP polypeptide, by a variety of methods, including enzyme linked immunosorbent assays (ELISAs), Western blots, immunoprecipitations and immunofluorescence. A test sample from an individual is assessed for the  
10 presence of an alteration in the expression and/or an alteration in composition of the polypeptide encoded by a FLAP nucleic acid, or for the presence of a particular variant encoded by a FLAP nucleic acid. An alteration in expression of a polypeptide encoded by a FLAP nucleic acid can be, for example, an alteration in the quantitative polypeptide expression (*i.e.*, the amount of  
15 polypeptide produced); an alteration in the composition of a polypeptide encoded by a FLAP nucleic acid is an alteration in the qualitative polypeptide expression (*e.g.*, expression of an altered FLAP polypeptide or of a different splicing variant). In a preferred embodiment, diagnosis of a susceptibility to a disease or condition associated with FLAP is made by detecting a particular  
20 splicing variant encoded by that FLAP variant, or a particular pattern of splicing variants.

Both such alterations (quantitative and qualitative) can also be present. An “alteration” in the polypeptide expression or composition, refers to an alteration in expression or composition in a test sample, as compared with the  
25 expression or composition of polypeptide by a FLAP nucleic acid in a control sample. A control sample is a sample that corresponds to the test sample (*e.g.*, is from the same type of cells), and is from an individual who is not affected by the disease or a susceptibility to a disease or condition associated with a FLAP nucleic acid. An alteration in the expression or composition of the polypeptide  
30 in the test sample, as compared with the control sample, is indicative of a susceptibility to a disease or condition associated with FLAP (*e.g.*, MI, ACS, stroke or PAOD). Similarly, the presence of one or more different splicing

variants in the test sample, or the presence of significantly different amounts of different splicing variants in the test sample, as compared with the control sample, is indicative of a susceptibility to a disease or condition associated with a FLAP nucleic acid. Various means of examining expression or composition of the polypeptide encoded by a FLAP nucleic acid can be used, including:

5 spectroscopy, colorimetry, electrophoresis, isoelectric focusing and immunoassays (*e.g.*, David *et al.*, U.S. Pat. 4,376,110) such as immunoblotting (see also *Current Protocols in Molecular Biology*, particularly Chapter 10). For example, in one embodiment, an antibody capable of binding to the polypeptide

10 (*e.g.*, as described above), preferably an antibody with a detectable label, can be used. Antibodies can be polyclonal, or more preferably, monoclonal. An intact antibody, or a fragment thereof (*e.g.*, Fab or F(ab')<sub>2</sub>) can be used. The term "labeled", with regard to the probe or antibody, is intended to encompass direct labeling of the probe or antibody by coupling (*i.e.*, physically linking) a

15 detectable substance to the probe or antibody, as well as indirect labeling of the probe or antibody by reactivity with another reagent that is directly labeled. Examples of indirect labeling include detection of a primary antibody using a fluorescently labeled secondary antibody and end-labeling of a DNA probe with biotin such that it can be detected with fluorescently labeled streptavidin.

20 Western blotting analysis, using an antibody as described above that specifically binds to a polypeptide encoded by an altered FLAP (*e.g.*, by a FLAP having a SNP as shown in Table 13), or an antibody that specifically binds to a polypeptide encoded by a non-altered nucleic acid, or an antibody that specifically binds to a particular splicing variant encoded by a nucleic acid,

25 can be used to identify the presence in a test sample of a particular splicing variant or of a polypeptide encoded by a polymorphic or altered FLAP, or the absence in a test sample of a particular splicing variant or of a polypeptide encoded by a non-polymorphic or non-altered nucleic acid. The presence of a polypeptide encoded by a polymorphic or altered nucleic acid, or the absence of

30 a polypeptide encoded by a non-polymorphic or non-altered nucleic acid, is diagnostic for a susceptibility to a disease or condition associated with FLAP, as

is the presence (or absence) of particular splicing variants encoded by the FLAP nucleic acid.

In one embodiment of this method, the level or amount of polypeptide encoded by a FLAP nucleic acid in a test sample is compared with the level or amount of the polypeptide encoded by the FLAP in a control sample. A level or amount of the polypeptide in the test sample that is higher or lower than the level or amount of the polypeptide in the control sample, such that the difference is statistically significant, is indicative of an alteration in the expression of the polypeptide encoded by the FLAP, and is diagnostic for a susceptibility to a disease or condition associated with that FLAP. Alternatively, the composition of the polypeptide encoded by a FLAP nucleic acid in a test sample is compared with the composition of the polypeptide encoded by the FLAP in a control sample (*e.g.*, the presence of different splicing variants). A difference in the composition of the polypeptide in the test sample, as compared with the composition of the polypeptide in the control sample, is diagnostic for a susceptibility to a disease or condition associated with that FLAP. In another embodiment, both the level or amount and the composition of the polypeptide can be assessed in the test sample and in the control sample. A difference in the amount or level of the polypeptide in the test sample, compared to the control sample; a difference in composition in the test sample, compared to the control sample; or both a difference in the amount or level, and a difference in the composition, is indicative of a susceptibility to a disease or condition associated with FLAP (*e.g.*, MI).

The invention further pertains to a method for the diagnosis and identification of susceptibility to myocardial infarction, ACS, stroke or PAOD in an individual, by identifying an at-risk haplotype in FLAP. In one embodiment, the at-risk haplotype is one which confers a significant risk of MI, ACS, stroke or PAOD. In one embodiment, significance associated with a haplotype is measured by an odds ratio. In a further embodiment, the significance is measured by a percentage. In one embodiment, a significant risk is measured as an odds ratio of at least about 1.2, including by not limited to: 1.2, 1.3, 1.4, 1.5, 1.6, 1.7, 1.8, and 1.9. In a further embodiment, an odds ratio



of at least 1.2 is significant. In a further embodiment, an odds ratio of at least about 1.5 is significant. In a further embodiment, a significant increase in risk is at least about 1.7 is significant. In a further embodiment, a significant increase in risk is at least about 20%, including but not limited to about 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95, and 98%. In a further embodiment, a significant increase in risk is at least about 50%. In yet another embodiment, an at-risk haplotype has a  $p$  value  $< 0.05$ . It is understood however, that identifying whether a risk is medically significant may also depend on a variety of factors, including the specific disease, the haplotype, and often, environmental factors.

The invention also pertains to methods of diagnosing a susceptibility to myocardial infarction, ACS, stroke or PAOD in an individual, comprising screening for an at-risk haplotype in the FLAP nucleic acid that is more frequently present in an individual susceptible to myocardial infarction (affected), compared to the frequency of its presence in a healthy individual (control), wherein the presence of the haplotype is indicative of susceptibility to myocardial infarction. Standard techniques for genotyping for the presence of SNPs and/or microsatellite markers that are associated with myocardial infarction, ACS, stroke or PAOD can be used, such as fluorescent based techniques (Chen, *et al.*, *Genome Res.* 9, 492 (1999), PCR, LCR, Nested PCR and other techniques for nucleic acid amplification. In a preferred embodiment, the method comprises assessing in an individual the presence or frequency of SNPs and/or microsatellites in the FLAP nucleic acid that are associated with myocardial infarction, ACS, stroke or PAOD, wherein an excess or higher frequency of the SNPs and/or microsatellites compared to a healthy control individual is indicative that the individual is susceptible to myocardial infarction, ACS, stroke or PAOD. See Table 7 for SNPs that comprise haplotypes that can be used as screening tools. See also Table 13 that sets forth SNPs and markers for use as screening tools.

In one embodiment, the at-risk haplotype is characterized by the presence of polymorphism(s) represented in Table 13. For example, SG13S99, where the SNP can be a "C" or a "T"; SG13S25, where the SNP can be a "G" or

an "A"; SG13S377, where the SNP can be a "G" or an "A"; SG13S106, where the SNP can be a "G" or an "A"; SG13S114, where the SNP can be a "T" or an "A"; SG13S89, where the SNP can be a "G" or an "A"; SG13S30, where the SNP can be a "G" or a "T"; SG13S32, where the SNP can be a "C" or an "A";  
5 SG13S42, where the SNP can be a "G" or an "A"; and SG13S35, where the SNP can be a "G" or an "A".

Kits (*e.g.*, reagent kits) useful in the methods of diagnosis comprise components useful in any of the methods described herein, including for example, hybridization probes or primers as described herein (*e.g.*, labeled  
10 probes or primers), reagents for detection of labeled molecules, restriction enzymes (*e.g.*, for RFLP analysis), allele-specific oligonucleotides, antibodies which bind to altered or to non-altered (native) FLAP polypeptide, means for amplification of nucleic acids comprising a FLAP, or means for analyzing the nucleic acid sequence of a nucleic acid described herein, or for analyzing the  
15 amino acid sequence of a polypeptide as described herein, etc. In one embodiment, a kit for diagnosing susceptibility to MI, ACS, stroke or PAOD can comprise primers for nucleic acid amplification of a region in the FLAP nucleic acid comprising an at-risk haplotype that is more frequently present in an individual having MI, ACS, stroke or PAOD or susceptible to MI, ACS,  
20 stroke or PAOD. The primers can be designed using portions of the nucleic acids flanking SNPs that are indicative of MI. In a particularly preferred embodiment, the primers are designed to amplify regions of the FLAP nucleic acid associated with an at-risk haplotype for MI, ACS, stroke or PAOD, as shown in Table 7, or more particularly the haplotype defined by the following  
25 SNP markers: In one embodiment, a haplotype associated with a susceptibility to myocardial infarction, ACS, stroke or PAOD comprises markers SG13S99, SG13S25, SG13S377, SG13S106, SG13S32 and SG13S35 at the 13q12-13 locus. In one particular embodiment, the presence of the alleles T, G, G, G, A and G at SG13S99, SG13S25, SG13S377, SG13S106, SG13S32 and SG13S35,  
30 respectively (the B6 haplotype), is diagnostic of susceptibility to myocardial infarction, ACS, stroke or PAOD. In another embodiment, a haplotype associated with a susceptibility to myocardial infarction, ACS, stroke or PAOD

comprises markers SG13S99, SG13S25, SG13S106, SG13S30 and SG13S42 at the 13q12-13 locus. In one particular embodiment, the presence of the alleles T, G, G, G and A at SG13S99, SG13S25, SG13S106, SG13S30 and SG13S42, respectively (the B5 haplotype), is diagnostic of susceptibility to myocardial infarction, ACS, stroke or PAOD. In a third embodiment, a haplotype associated with a susceptibility to myocardial infarction, ACS, stroke or PAOD comprises markers SG13S25, SG13S106, SG13S30 and SG13S42 at the 13q12-13 locus. In one particular embodiment, the presence of the alleles G, G, G and A at SG13S25, SG13S106, SG13S30 and SG13S42, respectively (the B4 haplotype), is diagnostic of susceptibility to myocardial infarction, ACS, stroke or PAOD. In a fourth embodiment, a haplotype associated with a susceptibility to myocardial infarction, ACS, stroke or PAOD comprises markers SG13S99, SG13S25, SG13S114, SG13S89 and SG13S32 at the 13q12-13 locus. In one particular embodiment, the presence of the alleles T, G, T, G and A at SG13S99, SG13S25, SG13S114, SG13S89 and SG13S32, respectively (the A5 haplotype), is diagnostic of susceptibility to myocardial infarction, ACS, stroke or PAOD. In a fifth embodiment, a haplotype associated with a susceptibility to myocardial infarction, ACS, stroke or PAOD comprises markers SG13S25, SG13S114, SG13S89 and SG13S32 at the 13q12-12 locus. In one particular embodiment, the presence of the alleles G, T, G and A at SG13S25, SG13S114, SG13S89 and SG13S32, respectively (the A4 haplotype), is diagnostic of susceptibility to myocardial infarction, ACS, stroke or PAOD.

#### SCREENING ASSAYS AND AGENTS IDENTIFIED THEREBY

The invention provides methods (also referred to herein as “screening assays”) for identifying the presence of a nucleotide that hybridizes to a nucleic acid of the invention, as well as for identifying the presence of a polypeptide encoded by a nucleic acid of the invention. In one embodiment, the presence (or absence) of a nucleic acid molecule of interest (*e.g.*, a nucleic acid that has significant homology with a nucleic acid of the invention) in a sample can be assessed by contacting the sample with a nucleic acid comprising a nucleic acid of the invention (*e.g.*, a nucleic acid having the sequence of one of SEQ ID

NOs: 1 or 3 or the complement thereof, or a nucleic acid encoding an amino acid having the sequence of SEQ ID NO: 2, or a fragment or variant of such nucleic acids), under stringent conditions as described above, and then assessing the sample for the presence (or absence) of hybridization. In a preferred embodiment, high stringency conditions are conditions appropriate for selective hybridization. In another embodiment, a sample containing a nucleic acid molecule of interest is contacted with a nucleic acid containing a contiguous nucleic acid sequence (*e.g.*, a primer or a probe as described above) that is at least partially complementary to a part of the nucleic acid molecule of interest (*e.g.*, a FLAP nucleic acid), and the contacted sample is assessed for the presence or absence of hybridization. In a preferred embodiment, the nucleic acid containing a contiguous nucleic acid sequence is completely complementary to a part of the nucleic acid molecule of interest.

In any of these embodiments, all or a portion of the nucleic acid of interest can be subjected to amplification prior to performing the hybridization.

In another embodiment, the presence (or absence) of a polypeptide of interest, such as a polypeptide of the invention or a fragment or variant thereof, in a sample can be assessed by contacting the sample with an antibody that specifically hybridizes to the polypeptide of interest (*e.g.*, an antibody such as those described above), and then assessing the sample for the presence (or absence) of binding of the antibody to the polypeptide of interest.

In another embodiment, the invention provides methods for identifying agents (*e.g.*, fusion proteins, polypeptides, peptidomimetics, prodrugs, receptors, binding agents, antibodies, small molecules or other drugs, or ribozymes which alter (*e.g.*, increase or decrease) the activity of the polypeptides described herein, or which otherwise interact with the polypeptides herein. For example, such agents can be agents which bind to polypeptides described herein (*e.g.*, binding agent for members of the leukotriene pathway, such as FLAP binding agents); which have a stimulatory or inhibitory effect on, for example, activity of polypeptides of the invention; or which change (*e.g.*, enhance or inhibit) the ability of the polypeptides of the invention to interact with members of the leukotriene pathway binding agents (*e.g.*, receptors or

other binding agents); or which alter posttranslational processing of the leukotriene pathway member polypeptide, such as a FLAP polypeptide (*e.g.*, agents that alter proteolytic processing to direct the polypeptide from where it is normally synthesized to another location in the cell, such as the cell surface; agents that alter proteolytic processing such that more polypeptide is released from the cell, etc.)

In one embodiment, the invention provides assays for screening candidate or test agents that bind to or modulate the activity of polypeptides described herein (or biologically active portion(s) thereof), as well as agents identifiable by the assays. Test agents can be obtained using any of the numerous approaches in combinatorial library methods known in the art, including: biological libraries; spatially addressable parallel solid phase or solution phase libraries; synthetic library methods requiring deconvolution; the “one-bead one-compound” library method; and synthetic library methods using affinity chromatography selection. The biological library approach is limited to polypeptide libraries, while the other four approaches are applicable to polypeptide, non-peptide oligomer or small molecule libraries of compounds (Lam, K.S., *Anticancer Drug Des.* 12:145 (1997)).

In one embodiment, to identify agents which alter the activity of a FLAP polypeptide, a cell, cell lysate, or solution containing or expressing a FLAP polypeptide (*e.g.*, SEQ ID NO: 2 or another splicing variant encoded by a FLAP nucleic acid, such as a nucleic acid comprising a SNP as shown in Table 13), or a fragment or derivative thereof (as described above), can be contacted with an agent to be tested; alternatively, the polypeptide can be contacted directly with the agent to be tested. The level (amount) of FLAP activity is assessed (*e.g.*, the level (amount) of FLAP activity is measured, either directly or indirectly), and is compared with the level of activity in a control (*i.e.*, the level of activity of the FLAP polypeptide or active fragment or derivative thereof in the absence of the agent to be tested). If the level of the activity in the presence of the agent differs, by an amount that is statistically significant, from the level of the activity in the absence of the agent, then the agent is an agent that alters the activity of a FLAP polypeptide. An increase in the level of FLAP activity in the

presence of the agent relative to the activity in the absence of the agent, indicates that the agent is an agent that enhances FLAP activity. Similarly, a decrease in the level of FLAP activity in the presence of the agent, relative to the activity in the absence of the agent, indicates that the agent is an agent that inhibits FLAP activity. In another embodiment, the level of activity of a FLAP polypeptide or derivative or fragment thereof in the presence of the agent to be tested, is compared with a control level that has previously been established. A statistically significant difference in the level of the activity in the presence of the agent from the control level indicates that the agent alters FLAP activity.

The present invention also relates to an assay for identifying agents which alter the expression of a FLAP nucleic acid (*e.g.*, antisense nucleic acids, fusion proteins, polypeptides, peptidomimetics, prodrugs, receptors, binding agents, antibodies, small molecules or other drugs, or ribozymes; which alter (*e.g.*, increase or decrease) expression (*e.g.*, transcription or translation) of the nucleic acid or which otherwise interact with the nucleic acids described herein, as well as agents identifiable by the assays. For example, a solution containing a nucleic acid encoding a FLAP polypeptide (*e.g.*, a FLAP nucleic acid) can be contacted with an agent to be tested. The solution can comprise, for example, cells containing the nucleic acid or cell lysate containing the nucleic acid; alternatively, the solution can be another solution that comprises elements necessary for transcription/translation of the nucleic acid. Cells not suspended in solution can also be employed, if desired. The level and/or pattern of FLAP expression (*e.g.*, the level and/or pattern of mRNA or of protein expressed, such as the level and/or pattern of different splicing variants) is assessed, and is compared with the level and/or pattern of expression in a control (*i.e.*, the level and/or pattern of the FLAP expression in the absence of the agent to be tested). If the level and/or pattern in the presence of the agent differ, by an amount or in a manner that is statistically significant, from the level and/or pattern in the absence of the agent, then the agent is an agent that alters the expression of the FLAP nucleic acid. Enhancement of FLAP expression indicates that the agent is an activator of FLAP activity. Similarly, inhibition of FLAP expression indicates that the agent is a repressor of FLAP activity.

In another embodiment, the level and/or pattern of FLAP polypeptide(s) (*e.g.*, different splicing variants) in the presence of the agent to be tested, is compared with a control level and/or pattern that have previously been established. A level and/or pattern in the presence of the agent that differs from  
5 the control level and/or pattern by an amount or in a manner that is statistically significant indicates that the agent alters FLAP expression.

In another embodiment of the invention, agents which alter the expression of a FLAP nucleic acid or which otherwise interact with the nucleic acids described herein, can be identified using a cell, cell lysate, or solution  
10 containing a nucleic acid encoding the promoter region of the FLAP nucleic acid operably linked to a reporter gene. After contact with an agent to be tested, the level of expression of the reporter gene (*e.g.*, the level of mRNA or of protein expressed) is assessed, and is compared with the level of expression in a control (*i.e.*, the level of the expression of the reporter gene in the absence of the  
15 agent to be tested). If the level in the presence of the agent differs, by an amount or in a manner that is statistically significant, from the level in the absence of the agent, then the agent is an agent that alters the expression of the FLAP nucleic acid, as indicated by its ability to alter expression of a nucleic acid that is operably linked to the FLAP nucleic acid promoter.

Enhancement of the expression of the reporter indicates that the agent is  
20 an activator of FLAP expression. Similarly, inhibition of the expression of the reporter indicates that the agent is a repressor of FLAP expression. In another embodiment, the level of expression of the reporter in the presence of the test agent, is compared with a control level that has previously been established. A  
25 level in the presence of the agent that differs from the control level by an amount or in a manner that is statistically significant indicates that the agent alters expression.

Agents which alter the amounts of different splicing variants encoded by a FLAP nucleic acid (*e.g.*, an agent which enhances expression of a first  
30 splicing variant, and which inhibits expression of a second splicing variant), as well as agents which stimulate activity of a first splicing variant and inhibit

activity of a second splicing variant, can easily be identified using these methods described above.

In other embodiments of the invention, assays can be used to assess the impact of a test agent on the activity of a polypeptide relative to a FLAP binding agent. For example, a cell that expresses a compound that interacts with a FLAP nucleic acid (herein referred to as a “FLAP binding agent”, which can be a polypeptide or other molecule that interacts with a FLAP nucleic acid, such as a receptor, or another molecule, such as 5-LO) is contacted with a FLAP in the presence of a test agent, and the ability of the test agent to alter the interaction between the FLAP and the FLAP binding agent is determined. Alternatively, a cell lysate or a solution containing the FLAP binding agent, can be used. An agent which binds to the FLAP or the FLAP binding agent can alter the interaction by interfering with, or enhancing the ability of the FLAP to bind to, associate with, or otherwise interact with the FLAP binding agent. Determining the ability of the test agent to bind to a FLAP nucleic acid or a FLAP nucleic acid binding agent can be accomplished, for example, by coupling the test agent with a radioisotope or enzymatic label such that binding of the test agent to the polypeptide can be determined by detecting the labeled with  $^{125}\text{I}$ ,  $^{35}\text{S}$ ,  $^{14}\text{C}$  or  $^3\text{H}$ , either directly or indirectly, and the radioisotope detected by direct counting of radioemmission or by scintillation counting. Alternatively, test agents can be enzymatically labeled with, for example, horseradish peroxidase, alkaline phosphatase, or luciferase, and the enzymatic label detected by determination of conversion of an appropriate substrate to product. It is also within the scope of this invention to determine the ability of a test agent to interact with the polypeptide without the labeling of any of the interactants. For example, a microphysiometer can be used to detect the interaction of a test agent with a FLAP or a FLAP binding agent without the labeling of either the test agent, FLAP, or the FLAP binding agent. McConnell, H.M. *et al.*, *Science* 257:1906-1912 (1992). As used herein, a “microphysiometer” (*e.g.*, Cytosensor™) is an analytical instrument that measures the rate at which a cell acidifies its environment using a light-



addressable potentiometric sensor (LAPS). Changes in this acidification rate can be used as an indicator of the interaction between ligand and polypeptide.

Thus, these receptors can be used to screen for compounds that are agonists for use in treating a disease or condition associated with FLAP or a susceptibility to a disease or condition associated with FLAP, or antagonists for studying a susceptibility to a disease or condition associated with FLAP (*e.g.*, MI, ACS, stroke or PAOD). Drugs can be designed to regulate FLAP activation, that in turn can be used to regulate signaling pathways and transcription events of genes downstream or of proteins or polypeptides interacting with FLAP (*e.g.*, 5-LO).

In another embodiment of the invention, assays can be used to identify polypeptides that interact with one or more FLAP polypeptides, as described herein. For example, a yeast two-hybrid system such as that described by Fields and Song (Fields, S. and Song, O., *Nature* 340:245-246 (1989)) can be used to identify polypeptides that interact with one or more FLAP polypeptides. In such a yeast two-hybrid system, vectors are constructed based on the flexibility of a transcription factor that has two functional domains (a DNA binding domain and a transcription activation domain). If the two domains are separated but fused to two different proteins that interact with one another, transcriptional activation can be achieved, and transcription of specific markers (*e.g.*, nutritional markers such as His and Ade, or color markers such as lacZ) can be used to identify the presence of interaction and transcriptional activation. For example, in the methods of the invention, a first vector is used which includes a nucleic acid encoding a DNA binding domain and also a FLAP polypeptide, splicing variant, or fragment or derivative thereof, and a second vector is used which includes a nucleic acid encoding a transcription activation domain and also a nucleic acid encoding a polypeptide which potentially may interact with the FLAP polypeptide, splicing variant, or fragment or derivative thereof (*e.g.*, a FLAP polypeptide binding agent or receptor). Incubation of yeast containing the first vector and the second vector under appropriate conditions (*e.g.*, mating conditions such as used in the Matchmaker™ system from Clontech (Palo Alto, California, USA)) allows identification of colonies

that express the markers of interest. These colonies can be examined to identify the polypeptide(s) that interact with the FLAP polypeptide or fragment or derivative thereof. Such polypeptides may be useful as agents that alter the activity of expression of a FLAP polypeptide, as described above.

5           In more than one embodiment of the above assay methods of the present invention, it may be desirable to immobilize either the FLAP, the FLAP binding agent, or other components of the assay on a solid support, in order to facilitate separation of complexed from uncomplexed forms of one or both of the polypeptides, as well as to accommodate automation of the assay. Binding of a  
10       test agent to the polypeptide, or interaction of the polypeptide with a binding agent in the presence and absence of a test agent, can be accomplished in any vessel suitable for containing the reactants. Examples of such vessels include microtitre plates, test tubes, and micro-centrifuge tubes. In one embodiment, a fusion protein (*e.g.*, a glutathione-S-transferase fusion protein) can be provided  
15       which adds a domain that allows a FLAP nucleic acid or a FLAP binding agent to be bound to a matrix or other solid support.

          In another embodiment, modulators of expression of nucleic acid molecules of the invention are identified in a method wherein a cell, cell lysate, or solution containing a nucleic acid encoding a FLAP nucleic acid is contacted  
20       with a test agent and the expression of appropriate mRNA or polypeptide (*e.g.*, splicing variant(s)) in the cell, cell lysate, or solution, is determined. The level of expression of appropriate mRNA or polypeptide(s) in the presence of the test agent is compared to the level of expression of mRNA or polypeptide(s) in the absence of the test agent. The test agent can then be identified as a modulator  
25       of expression based on this comparison. For example, when expression of mRNA or polypeptide is greater (statistically significantly greater) in the presence of the test agent than in its absence, the test agent is identified as a stimulator or enhancer of the mRNA or polypeptide expression. Alternatively, when expression of the mRNA or polypeptide is less (statistically significantly  
30       less) in the presence of the test agent than in its absence, the test agent is identified as an inhibitor of the mRNA or polypeptide expression. The level of

mRNA or polypeptide expression in the cells can be determined by methods described herein for detecting mRNA or polypeptide.

In yet another embodiment, the invention provides methods for identifying agents (*e.g.*, fusion proteins, polypeptides, peptidomimetics, 5 prodrugs, receptors, binding agents, antibodies, small molecules or other drugs, or ribozymes) which alter (*e.g.*, increase or decrease) the activity of a member of leukotriene pathway binding agent, such as a FLAP binding agent (*e.g.*, 5-LO), as described herein. For example, such agents can be agents which have a stimulatory or inhibitory effect on, for example, the activity of a member of 10 leukotriene pathway binding agent, such as a FLAP binding agent; which change (*e.g.*, enhance or inhibit) the ability a member of leukotriene pathway binding agents, (*e.g.*, receptors or other binding agents) to interact with the polypeptides of the invention; or which alter posttranslational processing of the member of leukotriene pathway binding agent, (*e.g.*, agents that alter proteolytic 15 processing to direct the member of the leukotriene pathway binding agent from where it is normally synthesized to another location in the cell, such as the cell surface; agents that alter proteolytic processing such that more active binding agent is released from the cell, etc.).

For example, the invention provides assays for screening candidate or 20 test agents that bind to or modulate the activity of a member of the leukotriene pathway (or enzymatically active portion(s) thereof), as well as agents identifiable by the assays. As described above, test agents can be obtained using any of the numerous approaches in combinatorial library methods known in the art, including: biological libraries; spatially addressable parallel solid 25 phase or solution phase libraries; synthetic library methods requiring deconvolution; the “one-bead one-compound” library method; and synthetic library methods using affinity chromatography selection. The biological library approach is limited to polypeptide libraries, while the other four approaches are applicable to polypeptide, non-peptide oligomer or small molecule libraries of 30 compounds (Lam, K.S. *Anticancer Drug Des.*, 12:145 (1997)).

In one embodiment, to identify agents which alter the activity of a member of the leukotriene pathway (such as a FLAP binding agent, or an agent

which binds to a member of the leukotriene pathway (a “binding agent”), a cell, cell lysate, or solution containing or expressing a binding agent (*e.g.*, 5-LO, or a leukotriene pathway member receptor, or other binding agent), or a fragment (*e.g.*, an enzymatically active fragment) or derivative thereof, can be contacted with an agent to be tested; alternatively, the binding agent (or fragment or derivative thereof) can be contacted directly with the agent to be tested. The level (amount) of binding agent activity is assessed (either directly or indirectly), and is compared with the level of activity in a control (*i.e.*, the level of activity in the absence of the agent to be tested). If the level of the activity in the presence of the agent differs, by an amount that is statistically significant, from the level of the activity in the absence of the agent, then the agent is an agent that alters the activity of the member of the leukotriene pathway. An increase in the level of the activity relative to a control, indicates that the agent is an agent that enhances (is an agonist of) the activity. Similarly, a decrease in the level of activity relative to a control, indicates that the agent is an agent that inhibits (is an antagonist of) the activity. In another embodiment, the level of activity in the presence of the agent to be tested, is compared with a control level that has previously been established. A level of the activity in the presence of the agent that differs from the control level by an amount that is statistically significant indicates that the agent alters the activity.

This invention further pertains to novel agents identified by the above-described screening assays. Accordingly, it is within the scope of this invention to further use an agent identified as described herein in an appropriate animal model. For example, an agent identified as described herein (*e.g.*, a test agent that is a modulating agent, an antisense nucleic acid molecule, a specific antibody, or a polypeptide-binding agent) can be used in an animal model to determine the efficacy, toxicity, or side effects of treatment with such an agent. Alternatively, an agent identified as described herein can be used in an animal model to determine the mechanism of action of such an agent.

Furthermore, this invention pertains to uses of novel agents identified by the above-described screening assays for treatments as described herein. In addition, an agent identified as described herein can be used to alter activity of a

polypeptide encoded by a FLAP nucleic acid, or to alter expression of a FLAP nucleic acid, by contacting the polypeptide or the nucleic acid (or contacting a cell comprising the polypeptide or the nucleic acid) with the agent identified as described herein.

5

The present invention is now illustrated by the following Examples, which are not intended to be limiting in any way. The teachings of all references cited are incorporated herein in their entirety.

#### EXAMPLE 1: IDENTIFICATION OF GENE AND HAPLOTYPES ASSOCIATED WITH MI

5           A genome wide scan of 296 multiplex Icelandic families with 713 MI  
patients was performed. Through the suggestive linkage to a locus on  
chromosome 13q12-13 for female MI patients and early onset MI patients, and  
haplotype association analysis, the gene encoding the 5-lipoxygenase activating  
protein (FLAP) was identified, and a 4-SNP haplotype within the gene was  
10       determined to confer a near 2-fold risk of MI. Male patients showed strongest  
association to the at-risk haplotype. Independent confirmation of FLAP  
association to MI was obtained in a British cohort of patients with sporadic MI.  
These findings support FLAP as the first specific gene isolated that confers  
substantial risk of the complex trait of MI.

15

## METHODS

### *Study population*

Patients entering the study were recruited from a registry that includes  
5 all MIs that occurred before the age of 75 (over 8,000 patients) in Iceland from  
1981 to 2000. This registry is a part of the World Health Organization  
MONICA Project (The World Health Organization MONICA Project, WHO  
MONICA Project Principal Investigators, *J Clin Epidemiol* **41**, 105-14 (1988)).  
Diagnoses of all patients in the registry followed strict diagnostic rules based on  
10 signs, symptoms, electrocardiograms, cardiac enzymes, and necropsy findings.

Genotypes from 713 MI patients and 1741 of their first-degree relatives  
were used in the linkage analysis. For the microsatellite association study of the  
MI locus, 802 unrelated MI patients (n=233 females, n=624 males and n= 302  
early onset) and 837 population-based controls were used. For the SNP  
15 association study in and around the FLAP gene 779 unrelated MI patients were  
genotyped (n=293 females, n=486 males and n=358 early onset). The control  
group for the SNP association study was population based and comprised of 628  
unrelated males and females in the age range of 30-85 years whose medical  
history was unknown.

20 The study was approved by the Data Protection Commission of Iceland  
and the National Bioethics Committee of Iceland. Informed consent was  
obtained from all study participants. Personal identifiers associated with  
medical information and blood samples were encrypted with a third party  
encryption system as previously described (Gulcher, J.R., Kristjansson, K.,  
25 Gudbjartsson, H. & Stefansson, K., *Eur J Hum Genet* **8**, 739-42 (2000)).

### *Statistical analysis*

A genome-wide scan was performed as previously described  
(Gretarsdottir, S. *et al. Am J Hum Genet* **70**, 593-603 (2002)), using a set of  
30 approximately 1000 microsatellite markers. Multipoint, affected-only allele-  
sharing methods (Kong, A. & Cox, N.J., *Am J Hum Genet* **61**, 1179-88 (1997))  
were used to assess the evidence for linkage. All results were obtained using

the program Allegro (Gudbjartsson, D.F., Jonasson, K., Frigge, M.L. & Kong, A. Allegro, *Nat Genet* 25, 12-3 (2000)) and the deCODE genetic map (Kong, A. *et al.*, *Nat Genet* 31, 241-7 (2002)). The  $S_{\text{pairs}}$  scoring function (Whittemore, A.S. & Halpern, J., *Biometrics* 50, 118-27 (1994); Kruglyak, L., Daly, M.J.,  
 5 Reeve-Daly, M.P. & Lander, E.S., *Am J Hum Genet* 58, 1347-63 (1996)) was used, as was the exponential allele-sharing model (Kong, A. & Cox, N.J. *Am J Hum Genet* 61, 1179-88 (1997)) to generate the relevant 1-df (degree of freedom) statistics. When combining the family scores to obtain an overall score, a weighting scheme was used that is halfway on a log scale between  
 10 weighting each affected pair equally and weighting each family equally. In the analysis, all genotyped individuals who are not affected are treated as “unknown”. Because of concern with small sample behaviour, corresponding P values were usually computed in two different ways for comparison, and the less significant one was reported. The first P value is computed based on large  
 15 sample theory;  $Z_{\text{lr}} = \sqrt{(2 \log_e (10) \text{ LOD})}$  and is distributed approximately as a standard normal distribution under the null hypothesis of no linkage (Kong, A. & Cox, N.J. *Am J Hum Genet* 61, 1179-88 (1997)). A second P value is computed by comparing the observed LOD score to its complete data sampling distribution under the null hypothesis (Gudbjartsson, D.F., Jonasson, K., Frigge,  
 20 M.L. & Kong, A. Allegro, *Nat Genet* 25, 12-3 (2000)). When a data set consists of more than a handful of families, these two P values tend to be very similar. The information measure that was used (Nicolae, D. University of Chicago (1999)), and is implemented in Allegro, is closely related to a classical measure of information (Dempster, A., Laird, NM, Rubin, DB., *J R Stat Soc B*  
 25 39, 1-38 (1977) and has a property that is between 0, if the marker genotypes are completely uninformative, and 1, if the genotypes determine the exact amount of allele sharing by descent among the affected relatives.

For single-marker association studies, Fisher’s exact test was used to calculate two-sided P values for each allele. All P values were unadjusted for  
 30 multiple comparisons unless specifically indicated. Allelic rather than carrier frequencies were presented for microsatellites, SNPs and haplotypes. To minimize any bias due to the relatedness of the patients that were recruited as



families for the linkage analysis first and second-degree relatives were eliminated from the patient list. For the haplotype analysis, the program NEMO was used (Gretarsdottir, S. *et al.*, *Nat Genet* **35**, 131-8 (2003)), which handles missing genotypes and uncertainty with phase through a likelihood procedure, using the expectation-maximization algorithm as a computational tool to estimate haplotype frequencies. Under the null hypothesis, the affected individuals and controls are assumed to have identical haplotype frequencies. Under the alternative hypotheses, the candidate at-risk haplotype is allowed to have a higher frequency in the affected individuals than in controls, while the ratios of frequencies of all other haplotypes are assumed to be the same in both groups. Likelihoods are maximized separately under both hypotheses, and a corresponding 1-df likelihood ratio statistic used to evaluate statistical significance (*id*). Even though searches were only performed for haplotypes that increase the risk, all reported P values are two-sided unless otherwise stated. To assess the significance of the haplotype association corrected for multiple testing, a randomisation test was carried out using the same genotype data. The cohorts of affected individuals and controls were randomized, and the analysis was repeated. This procedure was repeated up to 1.000 times and the P value presented is the fraction of replications that produced a P value for a haplotype tested that is lower than or equal to the P value observed using the original patient and control cohorts.

For both single-marker and haplotype analysis, relative risk (RR) and population attributable risk was calculated assuming a multiplicative model (Terwilliger, J.D. & Ott, J. A., *Hum Hered* **42**, 337-46 (1992); Falk, C.T. & Rubinstein, P., *Ann Hum Genet* **51** ( Pt 3), 227-33 (1987)) in which the risk of the two alleles of haplotypes a person carries multiply. LD was calculated between pairs of SNPs using the standard definition of  $D'$  (Lewontin, R.C., *Genetics* **50**, 757-82 (1964)) and  $R^2$  (Hill, W.G. & Robertson, A., *Genetics* **60**, 615-28 (1968)). Using NEMO, frequencies of the two marker allele combinations are estimated by maximum likelihood, and deviation from linkage equilibrium is evaluated by a likelihood ratio test. When plotting all SNP combinations to elucidate the LD structure in a particular region,  $D'$  was plotted

in the upper left corner and the P value in the lower right corner. In the LD plots presented, the markers are plotted equidistantly rather than according to their physical positions.

5      *Identification of DNA polymorphisms.*

New polymorphic repeats (e.g., dinucleotide or trinucleotide repeats) were identified with the Sputnik program. For microsatellite alleles: the CEPH sample 1347-02 (Centre d'Etudes du Polymorphisme Humain, genomics repository) is used as a reference. The lower allele of each microsatellite in this sample is set at 0 and all other alleles in other samples are numbered according  
10 in relation to this reference. Thus allele 1 is 1 bp longer than the lower allele in the CEPH sample, allele 2 is 2 bp longer than the lower allele in the CEPH sample, allele 3 is 3 bp longer than the lower allele in the CEPH sample, allele 4 is 4 bp longer than the lower allele in the CEPH sample, allele -1 is 1 bp shorter  
15 than the lower allele in the CEPH sample, allele -2 is 2 bp shorter than the lower allele in the CEPH sample, and so on. Single nucleotide polymorphisms in the gene were detected by PCR sequencing exonic and intronic regions from patients and controls. Public single nucleotide polymorphisms were obtained from the NCBI SNP database. SNPs were genotyped using a method for  
20 detecting SNPs with fluorescent polarization template-directed dye-terminator incorporation (SNP-FP-TDI assay) (Chen, X., Zehnauer, B., Gnirke, A. & Kwok, P.Y., *Proc Natl Acad Sci U S A* 94, 10756-61. (1997)) and TaqMan assays (Applied Biosystems).

25

## RESULTS

### *Linkage analysis*

A genome wide scan was performed in search of MI susceptibility genes using a framework set of around 1000 microsatellite markers. The initial  
30 linkage analysis included 713 MI patients who fulfilled the WHO MONICA research criteria (The World Health Organization MONICA Project, WHO MONICA Project Principal Investigators, *J Clin Epidemiol* 41, 105-14 (1988))

and were clustered in 296 extended families. The linkage analysis was also repeated for early onset, male and female patients separately. Description of the number of patients and families in each analysis are provided in Table 1.

5

TABLE 1: Number of patients that cluster into families and the corresponding number of families used in the linkage analysis

Phenotype	Number of patients	Number of families	Number of pairs	Genotyped relatives <sup>a</sup>
All MI patients	713	296	863	1741
Males	575	248	724	1385
Females	140	56	108	366
Early onset	194	93	156	739

<sup>a</sup>Genotyped relatives were used to increase the information on IBD sharing among the patients in the linkage analysis

None of these analyses yielded a locus of genome-wide significance. However, the most promising LOD score (LOD = 2.86) was observed on chromosome 13q12-13  
10 for female MI patients at the peak marker D13S289 (data not shown). This locus also had the most promising LOD score (LOD = 2.03) for patients with early onset MI. After increasing the information on identity-by-descent sharing to over 90% by typing 14 additional microsatellite markers in a 30 centiMorgan (cM) region around D13S289, the LOD score from the female analysis dropped to 2.48 (P value = 0.00036), while the  
15 highest LOD score remained at D13S289 (FIG. 9.1).

*Microsatellite association study*

The 7.6 Mb region that corresponds to a drop of one in LOD score in the female MI linkage analysis, contains 40 known genes (Table 2).

20

Table 2: Genes residing within the one LOD drop region of the chromosome 13q12-13 linkage peak.

LL_Symbol	LL_gene_name
USP12L1	ubiquitin specific protease 12 like 1
RPL21	ribosomal protein L21
GTF3A	general transcription factor IIIA

MTIF3	mitochondrial translational initiation factor 3
PDZRN1	PDZ domain containing ring finger 1
MGC9850	hypothetical protein MGC9850
POLR1D	polymerase (RNA) I polypeptide D, 16kDa
GSH1	GS homeobox 1
IPF1	insulin promoter factor 1, homeodomain transcription factor
CDX2	caudal type homeo box transcription factor 2
FLT3	fms-related tyrosine kinase 3
LOC255967	hypothetical protein LOC255967
	fms-related tyrosine kinase 1 (vascular endothelial growth factor/vascular permeability factor receptor)
FLT1	
C13orf12	chromosome 13 open reading frame 12
LOC283537	hypothetical protein LOC283537
KIAA0774	KIAA0774 protein
	solute carrier family 7 (cationic amino acid transporter, y+ system), member 1
SLC7A1	
UBL3	ubiquitin-like 3
MGC2599	hypothetical protein MGC2599 similar to katanin p60 subunit A 1 2599
HMGB1	high-mobility group box 1
D13S106E	highly charged protein
<b>ALOX5AP</b>	<b>arachidonate 5-lipoxygenase-activating protein</b>
FLJ14834	hypothetical protein FLJ14834
MGC40178	hypothetical protein MGC40178
HSPH1	heat shock 105kDa/110kDa protein 1
B3GTL	beta 3-glycosyltransferase-like
	similar to G protein coupled receptor affecting testicular descent (H. sapiens)
GREAT	
LOC196549	similar to hypothetical protein FLJ20897
13CDNA73	hypothetical protein CG003
BRCA2	breast cancer 2, early onset
CG018	hypothetical gene CG018
PRO0297	PRO0297 protein
LOC88523	CG016
CG012	hypothetical gene CG012
CG030	hypothetical gene CG030
CG005	hypothetical protein from BCRA2 region
APRIN	androgen-induced proliferation inhibitor
KL	Klotho
STARD13	START domain containing 13
RFC3	replication factor C (activator 1) 3, 38kDa

To determine which gene in this region most likely contributes to MI, 120 microsatellite markers positioned within this region were typed, and a case-control

association study was performed using 802 unrelated MI patients and 837 population-based controls. The association study was also repeated for each of the three phenotypes that were used in the linkage study, i.e. early onset, male and female MI patients.

5       The initial association analysis was performed when the average spacing between microsatellite markers was approximately 100 kb. This analysis revealed several extended haplotypes composed of 4 and 5 microsatellite markers that were significantly associated with female MI (see FIGs 1 and 2, and Tables 13 and 14). A region common to all these extended haplotypes, is defined by markers DG13S166  
10   and D13S1238. This region included only one gene, the FLAP nucleic acid sequence. The two marker haplotype involving alleles 0 and -2 for markers DG13S166 and D13S1238, respectively, was found in excess in patients.

This was the first evidence that the FLAP gene might be involved in the pathogenesis of myocardial infarction.

15       Subsequent haplotype analysis that included more microsatellite markers (n=120) in the candidate region on chromosome 13q12-13, now with a marker density of 1 microsatellite marker per 60 kb, showed decreased significance of the original haplotype association. However, the haplotype association analysis using increased density of markers again pointed towards the FLAP gene. This analysis strongly  
20   suggested that a 300 kb region was involved in the susceptibility of myocardial infarction. As shown in FIG. 7.2, the haplotype that showed association to all MI with the lowest P value (0.00009) covered a region that contains 2 known genes, including the gene encoding arachidonate 5-lipoxygenase-activating protein (FLAP) and a gene with an unknown function called highly charged protein. However, the haplotype  
25   association to female MI in this region was less significant (P value =0.005) than for all MI patients and to our surprise, the most significant haplotype association was observed for male MI patients (P value = 0.000002). This male MI haplotype was the only haplotype that remained significant after adjusting for all haplotypes tested.

In view of the association results described above, FLAP was an attractive  
30   candidate and therefore efforts were focused on this gene.

*Screening for polymorphisms in FLAP and linkage disequilibrium mapping*

To determine whether variations within the FLAP gene significantly associate with MI and to search for causal variations, the FLAP gene was sequenced in 93 patients and 93 controls. The sequenced region covers 60 kb containing the FLAP gene, including the 5 known exons and introns and the 26 kb region 5' to the first exon and 7 kb region 3' to the fifth exon. In all, 144 SNPs were identified, of those 96 were excluded from further analysis either because of low minor allele frequency or they were completely correlated with other SNPs and thus redundant. FIG. 9 shows the distribution of the 48 SNPs, used for genotyping, relative to exons, introns and the 5' and 3' flanking regions of the FLAP gene. Only one SNP was identified within a coding sequence (exon 2). This SNP did not lead to amino acid substitution. The locations of these SNPs in the NCBI human genome assembly, build 34, are listed in Table 3.

Table 3: Locations of all genotyped SNPs in NCBI build 34 of the human genome assembly

SNP name	Build34 start
SG13S381	29083350
SG13S366	29083518
SG13S1	29086224
SG13S2	29087473
SG13S367	29088090
SG13S10	29088473
SG13S3	29089044
SG13S368	29089886
SG13S4	29090997
SG13S5	29091307
SG13S90	29091780
SG13S6	29092536
SG13S371	29093964
SG13S372	29094259
SG13S373	29096688
SG13S375	29096874
SG13S376	29096962
SG13S25	29097553
SG13S377	29101965
SG13S100	29104271
SG13S95	29106329
SG13S191	29107830
SG13S106	29108579

SG13S114	29110096
SG13S121	29112174
SG13S122	29112264
SG13S43	29112455
SG13S192	29116308
SG13S88	29116401
SG13S137	29118118
SG13S86	29118815
SG13S87	29118873
SG13S39	29119740
SG13S26	29122253
SG13S27	29122283
SG13S29	29123643
SG13S89	29124441
SG13S96	29124906
SG13S30	29125840
SG13S97	29129139
SG13S32	29130547
SG13S41	29134045
SG13S42	29135877
SG13S34	29137100
SG13S35	29138117
SG13S181	29138633
SG13S184	29139435
SG13S188	29140805

---

In addition to the SNPs, a polymorphism consisting of a monopolymer A repeat that has been described in the FLAP promoter region was typed (Koshino, T. *et al.*,  
5 *Mol Cell Biol Res Commun* **2**, 32-5 (1999)).

The linkage disequilibrium (LD) block structure defined by the 48 SNPs that were selected for further genotyping is shown in FIG. 11. A strong LD was detected across the FLAP region, although it appears that at least one recombination may have occurred dividing the region into two strongly correlated LD blocks.

#### 10 *Haplotype association to MI*

To perform a case-control association study the 48 selected SNPs and the monopolymer A repeat marker were genotyped in a set of 779 unrelated MI patients and 628 population-based controls. Each of the 49 markers were tested individually for association to the disease. Three SNPs, one located 3 kb upstream of the first exon and

the other two 1 and 3 kb downstream of the first exon, showed nominally significant association to MI (Table 4).

Table 4: SNP allelic association in the MI cohort

Phenotype	Marker	Allele	<i>P</i> value	RR	# Pat.	% Pat.	# Ctrl	% Ctrl
All patients	SG13S106	G	0.0044	1.29	681	72.0	530	66.6
	SG13S100	A	0.020	1.29	388	69.6	377	63.9
	SG13S114	T	0.021	1.21	764	70.0	602	65.8
Males	SG13S106	G	0.0037	1.35	422	72.9	530	66.6
	SG13S100	A	0.0099	1.36	292	70.7	377	63.9
	SG13S114	T	0.026	1.24	477	70.4	602	65.8
Early onset	SG13S100	A	0.0440	1.43	99	71.7	377	63.9

Nominally significant SNP association with corresponding number of patients

5 (# Pat.) and controls (#Ctrl). RR refers to relative risk.

However, after adjusting for the number of markers tested, these results were not significant. A search was then conducted for haplotypes that show association to the disease using the same cohorts. For computational reasons, the search was limited  
 10 to haplotype combinations constructed out of two, three or four SNPs and only haplotypes that were in excess in the patients were tested. The resulting *P* values were adjusted for all the haplotypes tested by randomizing the patients and controls (see Methods).

Several haplotypes were found that were significantly associated to the disease  
 15 with an adjusted *P* value less than 0.05 (Table 5).



TABLE 5: SNP haplotypes that significantly associate with Icelandic MI patients

SG13S4	SG13S6	SG13S372	SG13S25	SG13S377	SG13S100	SG13S95	SG13S114	SG13S192	SG13S137	SG13S86	SG13S87	SG13S39	SG13S27	SG13S89	SG13S96	SG13S32	SG13S41	SG13S42	SG13S34	SG13S188	<i>P</i> value <sup>a</sup>	<i>P</i> value <sup>b</sup>	Pat.fr q	Ctrl.fr q	RR	D' <sup>c</sup>
			G				T							G		A					0,0000023	0,005	0,158	0,095	1,80	1,00
			G				T			A						A					0,0000030	0,006	0,158	0,095	1,78	1,00
			G				T									A			T		0,0000032	0,007	0,157	0,094	1,79	1,00
			G		A					A						A					0,0000046	0,012	0,158	0,083	2,07	0,89
			G			T	T									A					0,0000047	0,012	0,154	0,093	1,78	1,00
			G				T			G						A					0,0000055	0,015	0,147	0,087	1,81	1,00
			G		A											A			T		0,0000061	0,017	0,157	0,083	2,07	0,89
			G		A									G		A					0,0000063	0,017	0,157	0,084	2,04	0,89
			G				T									A					0,0000070	0,021	0,157	0,096	1,76	1,00
			G				T								A	A					0,0000075	0,022	0,149	0,089	1,78	1,00
	G					T	T									A					0,0000083	0,024	0,208	0,139	1,62	0,99
			G		A					G						A					0,0000084	0,026	0,145	0,074	2,14	0,88
			G				T	A								A					0,0000084	0,026	0,139	0,082	1,82	1,00
			G				T						G			A					0,0000091	0,028	0,156	0,096	1,75	1,00
	G						T									A			T		0,0000094	0,028	0,210	0,141	1,61	0,99
	G		G				T									A					0,0000100	0,028	0,156	0,096	1,74	1,00
	G				A											A			A		0,0000101	0,028	0,215	0,133	1,80	0,81
			G		A											A					0,0000105	0,028	0,157	0,084	2,03	0,89
	G				A					A						A					0,0000108	0,029	0,214	0,133	1,78	0,81
			G		A										A	A					0,0000110	0,030	0,146	0,075	2,10	0,88
	G						T			A						A					0,0000112	0,030	0,212	0,144	1,60	1,00
			G		A			A											T		0,0000113	0,030	0,151	0,081	2,03	0,78
			G				T						G			A					0,0000118	0,031	0,156	0,096	1,73	1,00
	G				A											A			T		0,0000126	0,034	0,212	0,131	1,79	0,79
	G						T							G		A					0,0000129	0,035	0,211	0,144	1,59	1,00
			G		A								G			A					0,0000134	0,035	0,156	0,084	2,01	0,89
	G						T									A					0,0000136	0,036	0,211	0,143	1,60	1,00
	G		G		A											A					0,0000137	0,036	0,156	0,085	2,00	0,89
			G		A			A							A						0,0000148	0,037	0,151	0,081	2,01	0,78
			G				T	A											T		0,0000150	0,037	0,160	0,099	1,73	0,87
			G		A			A								A					0,0000150	0,037	0,130	0,066	2,13	0,90
			G				T		C										T		0,0000154	0,039	0,152	0,094	1,73	0,93
			G				T									A		A			0,0000154	0,040	0,155	0,097	1,70	1,00
			G				T		C							A					0,0000157	0,040	0,141	0,085	1,76	1,00
			G	G	A											A					0,0000158	0,040	0,152	0,084	1,94	0,90
	G						T						G			A					0,0000163	0,040	0,210	0,143	1,59	0,99
	G						T			G						A					0,0000166	0,041	0,200	0,134	1,61	0,92
	G				A									G		A					0,0000168	0,042	0,213	0,133	1,76	0,81

		G	A						G			A				0,0000168	0,042	0,156	0,084	2,00	0,89
C	G		A									A				0,0000171	0,042	0,211	0,136	1,70	0,81
	G				T	A						A				0,0000183	0,043	0,192	0,128	1,62	0,85
	G		A									A				0,0000184	0,043	0,212	0,132	1,77	0,81
	G				T							A		T		0,0000193	0,046	0,328	0,251	1,46	0,99
		G			T				G					T		0,0000194	0,046	0,175	0,115	1,64	0,98
	G	G		A								A				0,0000202	0,048	0,210	0,136	1,70	0,81
	G	G	A		A											0,0000209	0,049	0,151	0,082	2,00	0,76

<sup>a</sup> Single test P values. <sup>b</sup> P values adjusted for all the SNP haplotypes tested.

<sup>c</sup> Measure of correlation with Haplotype A4 .

The most significant association was observed for a four SNP haplotype spanning 33 kb, including the first four exons of the gene (Fig. 9.3), with a nominal *P* value of 0.0000023 and an adjusted *P* value of 0.005. This haplotype, labelled A4, has  
 5 haplotype frequency of 15.8% (carrier frequency 30.3%) in patients versus 9.5% (carrier frequency 17.9%) in controls (Table 6).

Table 6: Association of the A4 haplotype to MI, Stroke and PAOD

Phenotype (n)	Frq. Pat.	RR	PAR	<i>P</i> -value	<i>P</i> -value <sup>a</sup>
<i>MI</i> (779)	0.158	1.80	0.135	0.0000023	0.005
Males (486)	0.169	1.95	0.158	0.00000091	ND <sup>b</sup>
Females (293)	0.138	1.53	0.094	0.0098	ND
Early onset (358)	0.138	1.53	0.094	0.0058	ND
<i>Stroke</i> (702) <sup>c</sup>	0.149	1.67	0.116	0.000095	ND
Males (373)	0.156	1.76	0.131	0.00018	ND
Females (329)	0.141	1.55	0.098	0.0074	ND
<i>PAOD</i> (577) <sup>c</sup>	0.122	1.31	0.056	0.061	ND
Males (356)	0.126	1.36	0.065	0.057	ND
Females (221)	0.114	1.22	0.041	0.31	ND

<sup>a</sup> *P* value adjusted for the number of haplotypes tested. <sup>b</sup>Not done. <sup>c</sup>Excluding known cases of MI. Shown is the FLAP A4 haplotype and corresponding number of patients (n), haplotype frequency in patients (Frq. pat.), relative risk (RR), population attributed risk (PAR) and *P* values. The A4 haplotype is defined by the following SNPs: SG13S25, SG13S114, SG13S89 and SG13S32 (Table 5). The same controls (n=628) are used for the association analysis in MI, stroke and PAOD as well as for the male, female and early onset analysis. The A4 haplotype frequency in the control cohort is 0.095.

10

The relative risk conferred by The A4 haplotype compared to other haplotypes constructed out of the same SNPs, assuming a multiplicative model, was 1.8 and the corresponding population attributable risk (PAR) was 13.5%. As shown in Table 6, the  
 15 A4 haplotype was observed in higher frequency in male patients (carrier frequency

30.9%) than in female patients (carrier frequency 25.7%). All the other haplotypes that were significantly associated with an adjusted P value less than 0.05, were highly correlated with the A4 haplotype and should be considered variants of that haplotype (Table 5). Table 6 shows the results of the haplotype A4 association study using 779  
 5 MI patients, 702 stroke patients, 577 PAOD patients and 628 controls. First and second degree relatives were excluded from the patient cohorts. All known cases of MI were removed from the stroke and PAOD cohorts before testing for association. A significant association of the A4 haplotype to stroke was observed, with a relative risk of 1.67 (P value = 0.000095). In addition, it was determined whether the A4 haplotype  
 10 was primarily associated with a particular sub-phenotype of stroke, and found that both ischemic and hemorrhagic stroke were significantly associated with the A4 haplotype (Table 22, below).

#### More variants of haplotype A4

15 Two correlated series of SNP haplotypes were observed in excess in patients, denoted as A and B in Table 7. The length of the haplotypes varies between 33 and 69 Kb, and the haplotypes cover one or two blocks of linkage disequilibrium. Both series of haplotypes contain the common allele G of the SNP SG13S25. All haplotypes in the A series contain the SNP SG13S114, while all haplotypes in the B series contain the  
 20 SNP SG13S106. In the B series, the haplotypes B4, B5, and B6 have a relative risk (RR) greater than 2 and with allelic frequencies above 10%. The haplotypes in A series have slightly lower RR and lower p-values, but higher frequency (15-16%). The haplotypes in series B and A are strongly correlated, i.e. the haplotypes in B define a subset of the haplotypes in A. Hence, haplotypes B are more specific than A.  
 25 Haplotypes A are however more sensitive, i.e. they capture more individuals with the putative mutation, as is observed in the population attributable risk which is less for B than for A. Furthermore, these haplotypes show similar risk ratios and allelic frequency for early-onset patients (defined as onset of first MI before the age of 55) and for both gender. In addition, analyzing various groups of patients with known risk  
 30 factors, such as hypertension, high cholesterol, smoking and diabetes, did not reveal any significant correlation with these haplotypes, indicating that the haplotypes in the FLAP gene represent an independent genetic susceptibility factor for MI.

Table 7: The selected SNP haplotypes and the corresponding p-values

	p-val	RR	#aff	aff.frq.	carr.frq.	#con	con.frq.	PAR	SG13S99	SG13S25	SG13S377	SG13S106	SG13S114	SG13S89	SG13S30	SG13S32	SG13S42	SG13S35
B4	4.80E-05	2.08	903	0.106	0.2	619	0.054	0.11		G		G			G		A	
B5	2.40E-05	2.2	910	0.101	0.19	623	0.049	0.11	T	G		G			G		A	
B6	1.80E-06	2.22	913	0.131	0.24	623	0.063	0.14	T	G	G	G				A		G
A4	5.10E-06	1.81	919	0.159	0.29	623	0.095	0.14		G			T	G		A		
A5	2.60E-06	1.91	920	0.15	0.28	624	0.085	0.14	T	G			T	G		A		

Relative risk (RR), number of patients (#aff), allelic frequency in patients (aff.frq.), carrier frequency in patients (carr.frq.), number of controls (#con), allelic frequency in controls (con.frq.), population attributable risk (PAR). The patients used for this analysis were all unrelated within 4 meioses.

### Haplotype association to female MI

10

Before we had typed all the SNPs that eventually lead to the identification of A4 haplotype we performed a haplotype association analysis that included 437 female MI patients, 1049 male MI patients, and 811 controls that had been genotyped with several SNPs and 3 microsatellite markers. These markers were all located within 300 kb region encompassing the FLAP gene. In a case-control study of the MI patients using these data, several haplotypes were found, that were significantly over-represented in the female MI patients compared to controls (see Table 8). All these haplotypes were highly correlated with each other.

20 Table 8: haplotypes in the FLAP region (FLAP and flanking nucleotide sequences) that were associated with female MI.

SG13S421	SG13S418	SG13S419	SG13S420	DG13S166	SG13S106	SG13S114	SG13S121	SG13S122	SG13S88	SG13S181	SG13S184	D13S1238	DG13S2605	p-val	N <sub>aff</sub>	aff.frq	N <sub>ctrl</sub>	ctrl.frq	rel_risk	PAR	Info
----------	----------	----------	----------	----------	----------	----------	----------	----------	---------	----------	----------	----------	-----------	-------	------------------	---------	-------------------	----------	----------	-----	------

-135-

	C		T	0						G	-2		1.30E-05	455	0.108	811	0.048	2.4	0.122	0.615
	C		T	0		T		A	T		-2	0	7.61E-06	455	0.065	812	0.02	3.45	0.091	0.615
	C		T	0		T			T		-2	0	8.82E-06	455	0.065	812	0.02	3.47	0.092	0.602
	C		T	0		T	G		T		-2	0	9.31E-06	455	0.065	812	0.02	3.39	0.089	0.611
	C		T	0		T			T	G	-2	0	6.91E-06	455	0.063	812	0.019	3.54	0.09	0.624
	C	A	T	0		T			T		-2	0	9.76E-06	455	0.063	812	0.019	3.51	0.089	0.606
	C		T	0		T		A	T	G	-2		1.09E-05	455	0.063	811	0.019	3.41	0.086	0.618
	C		T	0		T			T	G	-2	0	1.10E-05	455	0.063	812	0.019	3.44	0.087	0.611
	C		T	0			G		T	G	-2	0	1.11E-05	455	0.063	812	0.018	3.56	0.086	0.589
	C		T	0			G		T	G	-2		1.22E-05	455	0.063	811	0.018	3.6	0.087	0.577
	C		T	0	G				T	G	-2	0	1.26E-05	455	0.063	812	0.02	3.35	0.088	0.629
	C		T	0				A	T	G	-2	0	8.59E-06	455	0.062	812	0.018	3.53	0.085	0.62
	C		T	0				A	T	G	-2		1.20E-05	455	0.062	811	0.019	3.42	0.086	0.617
	C		T	0			G	A	T	G	-2		1.21E-05	455	0.062	811	0.019	3.43	0.086	0.619
A	C		T	0			G		T	G	-2		7.93E-06	455	0.061	811	0.016	3.95	0.088	0.562
A	C		T	0					T	G	-2		1.09E-05	455	0.061	811	0.017	3.85	0.09	0.56
A	C		T	0		T			T	G	-2		5.00E-06	455	0.06	811	0.015	4.11	0.087	0.576
	C	A	T	0			G		T	G	-2		1.31E-05	455	0.06	811	0.017	3.66	0.085	0.586
A	C		T	0				A	T	G	-2		8.53E-06	455	0.059	811	0.016	3.85	0.085	0.593
A	C	A	T	0					T	G	-2		9.63E-06	455	0.058	811	0.015	4.03	0.085	0.565

Table 9 shows two haplotypes that are representative of these female MI risk haplotypes. The relative risk of these haplotypes were 2.4 and 4, and they were carried by 23% and 13% of female MI patients, respectively.

Table 9: Two representative variants of the female MI “at risk” haplotypes

	SG13S418	SG13S420	DG13S166	SG13S114	SG13S88	SG13S184	D13S1238	p-val	N aff	aff.frq	N ctrl	ctrl.frq	rel_risk	PAR	info
Female MI															
	C	T	0	T	T	G	-2	6.38E-06	4549	0.05	8095	0.01	4.0	0.08	0.57
	C	T	0			G	-2	2.74E-05	4476	0.10	8098	0.04	2.3	0.11	0.62

**P-val:** p-value for the association. **N\_aff:** Number of patients used in the analysis. **Aff.frq:** haplotype frequency in patients. **N\_ctrl:** number of controls used in the analysis. **Ctrl.frq:** Haplotype frequency in controls. **Rel\_risk:** Relative risk of the haplotype. **PAR:** population attributable risk. **Info:** information content.

Table 10 shows that these same haplotypes were also over-represented in male MI patients compared to controls, although with lower relative risk. It should be noted that after typing and analysing more SNPs in the FLAP region these female MI “at risk” haplotypes could no longer be considered significant after adjusting for multiple testing.

Table 10: The frequencies of the female MI “at risk” haplotypes in male patients vs controls.

Cont. chr.																	
		SG13S418	SG13S420	DG13S166	SG13S114	SG13S88	SG13S184	D13S1238		p-val	N <sub>aff</sub>	aff.frq	N <sub>ctrl</sub>	ctrl.frq	rel_risk	PAR	Info
Male MI																	
	C T	0	T	T	G	-2	3.37E-01	1087	0.027	809	0.021	1.32	0.013	0.577			
	C T	0			G	-2	5.39E-01	1087	0.056	809	0.05	1.13	0.013	0.568			

10

**P-val:** p-value for the association. **N<sub>aff</sub>:** Number of patients used in the analysis. **Aff.frq:** haplotype frequency in patients. **N<sub>ctrl</sub>:** number of controls used in the analysis. **Ctrl.frq:** Haplotype frequency in controls. **Rel\_risk:** Relative risk of the haplotype. **PAR:** population attributable risk. **Info:** information content.

15

Table 11: The marker map for chromosome 13 used in the linkage analysis.

Location (cM)	Marker	Location (cM)	Marker
6	D13S175	63.9	D13S170
9.8	D13S1243	68.7	D13S265
13.5	D13S1304	73	D13S167
17.2	D13S217	76.3	D13S1241
21.5	D13S289	79.5	D13S1298
25.1	D13S171	81.6	D13S1267
28.9	D13S219	84.7	D13S1256
32.9	D13S218	85.1	D13S158
38.3	D13S263	87	D13S274
42.8	D13S326	93.5	D13S173

45.6	D13S153	96.7	D13S778
49.4	D13S1320	102.7	D13S1315
52.6	D13S1296	110.6	D13S285
55.9	D13S156	115	D13S293
59.8	D13S1306		



Table 12 Marker Map for the second step of Linkage Analysis

Location (cM)	Marker	Location (cM)	Marker
1.758	D13S175	42.585	D13S1248
9.235	D13S787	44.288	D13S1233
11.565	D13S1243	44.377	D13S263
16.898	D13S221	45.535	D13S325
17.454	D13S1304	45.536	D13S1270
18.011	D13S1254	45.537	D13S1276
18.59	D13S625	49.149	D13S326
19.308	D13S1244	49.532	D13S1272
19.768	D13S243	52.421	D13S168
22.234	D13S1250	52.674	D13S287
22.642	D13S1242	60.536	D13S1320
22.879	D13S217	64.272	D13S1296
25.013	D13S1299	71.287	D13S156
28.136	D13S289	76.828	D13S1306
28.678	D13S290	77.86	D13S170
29.134	D13S1287	82.828	D13S265
30.073	D13S260	91.199	D13S1241
31.98	D13S171	93.863	D13S1298
32.859	D13S267	97.735	D13S779
33.069	D13S1293	100.547	D13S1256
33.07	D13S620	102.277	D13S274
34.131	D13S220	111.885	D13S173
36.427	D13S219	112.198	D13S796
39.458	D13S1808	115.619	D13S778
40.441	D13S218	119.036	D13S1315
41.113	D13S1288	126.898	D13S285
41.996	D13S1253	131.962	D13S293

Table 13 shows the exons with positions that encode the FLAP protein, markers, polymorphisms and SNPs identified within the genomic sequence by the methods described herein.

NCBI build34; start chr. (bp)	NCBI build34; on stop chr. 13 (bp)	SNP/marker/ exon name	alias1	alias2	public SNP	Variation
28932432	28932432	SG13S421		DG00AAFQR	rs1556428	A/G
28960356	28960356	SG13S417		SNP13B_R1028729	rs1028729	C/T
28965803	28965803	SG13S418		SNP13B_Y1323898	rs1323898	A/G
28974627	28974627	SG13S44				A/G
28975101	28975101	SG13S45				C/G
28975315	28975315	SG13S46				A/G
28975353	28975353	SG13S50				C/T
28975774	28975774	SG13S52				A/G
28985244	28985244	SG13S53			rs1408167	A/C
28985303	28985303	SG13S55			rs1408169	A/G
28985423	28985423	SG13S56				G/T
28985734	28985734	SG13S57			rs6490471	C/T
28985902	28985902	SG13S58			rs6490472	A/G
29003869	29003869	SG13S59				C/G
29004696	29004696	SG13S60				A/G
29007670	29007670	SG13S419		SNP13B_K912392	rs912392	C/T
29015410	29015410	SG13S61				C/T
29025792	29025792	SG13S62				C/T
29026202	29026202	SG13S63			rs7997114	A/G
29026668	29026668	SG13S64				A/G
29038707	29038707	SG13S65				A/G
29042180	29042180	SG13S420		DG00AAFIV	rs2248564	A/T
29049355	29049355	SG13S66				A/G
29049446	29049446	SG13S67				C/T
29050416	29050416	SG13S69				A/C
29059348	29059348	SG13S70				A/G
29059383	29059383	SG13S71				A/G
29059402	29059402	SG13S72				G/T
29063702	29063949	D13S289				
29064359	29064753	DG13S166				
29066272	29066272	SG13S73				A/G
29070551	29070551	SG13S99	SNP_13_Y1323892	DG00AAFIU	rs1323892	C/T
29081983	29081983	SG13S382	FLA267479			A/G
29082200	29082200	SG13S383	FLA267696			A/G
29082357	29082357	SG13S384	FLA267853			A/G
29083350	29083350	SG13S381	FLA268846	DG00AAJER		C/G
29083518	29083518	SG13S366	FLA269014	DG00AAJES	rs4312166	A/G
29085102	29085102	SG13S385	FLA270742			C/T
29085190	29085190	SG13S386	FLA270830			A/G
29086224	29086224	SG13S1	FLA271864			G/T
29087473	29087473	SG13S2	FLA273371			A/G
29088090	29088090	SG13S367	FLA273988	DG00AAJEU	rs4474551	A/G
29088186	29088186	SG13S388	FLA274084			A/G
29088473	29088473	SG13S10	FLA274371			A/T

29089044	29089044	SG13S3	FLA274942			C/T
29089886	29089886	SG13S368	FLA275784	DG00AAJEV		C/T
29090025	29090025	SG13S369	FLA275923	DG00AAJEW		G/T
29090054	29090054	SG13S370	FLA275952	DG00AAJEX		A/G
29090997	29090997	SG13S4	FLA276895			G/C
29091307	29091307	SG13S5	FLA277205		rs4238133	G/T
29091580	29091580	SG13S389	FLA277478			A/G
29091780	29091780	SG13S90	FLA277678			A/C
29092287	29092287	SG13S390	FLA278185		rs5004913	A/G
29092536	29092536	SG13S6	FLA278434			A/G
29092594	29092594	SG13S391	FLA278492			A/G
29092947	29092947	SG13S392	FLA278845			G/T
29093964	29093964	SG13S371	FLA279888	DG00AAJEY	rs4409939	A/G
29094259	29094259	SG13S372	FLA280183	DG00AAJEZ		A/G
29094999	29094999	SG13S393	FLA280923			A/T
29096688	29096688	SG13S373	FLA282612	DG00AAJFA		A/G
29096813	29096813	SG13S374	FLA282737	DG00AAJFB		A/G
29096874	29096874	SG13S375	FLA282798	DG00AAJFC		C/T
29096962	29096962	SG13S376	FLA282886	DG00AAJFD		A/G
29097476	29097476	SG13S394	FLA283400			C/G
29097553	29097553	SG13S25	FLA283477			A/G
29098486	29098486	SG13S395	FLA284410			A/G
29098891	29098891	SG13S396	FLA284815			A/C
29098979	29098979	SG13S397	FLA284903			C/T
29101965	29101965	SG13S377	FLA287889	DG00AAJFF		A/G
29103909	29103909	SG13S189	FLA289833			C/G
29104271	29104271	SG13S100	FLA290195	DG00AAHIK	rs4073259	A/G
29104629	29104629	SG13S398	FLA290553			C/G
29104646	29104646	SG13S94	FLA290570		rs4073261	C/T
29105099	29105099	SG13S101	FLA291023		rs4075474	C/T
29106329	29106329	SG13S95	FLA292253			G/T
29106652	29106652	SG13S102	FLA292576			A/T
29107138	29107138	SG13S103	FLA293062			C/T
29107404	29107404	SG13S104	FLA293328			A/G
29107668	29107812	EXON1				
29107830	29107830	SG13S191	FLA293754	DG00AAFJT	rs4769055	A/C
29108398	29108398	SG13S105	FLA294322			A/G
29108579	29108579	SG13S106	FLA294503	DG00AAHII		A/G
29108919	29108919	SG13S107	FLA294843		rs4075131	A/G
29108972	29108972	SG13S108	FLA294896		rs4075132	C/T
29109112	29109112	SG13S109	FLA295036			A/G
29109182	29109182	SG13S110	FLA295106			A/G
29109344	29109344	SG13S111	FLA295268		rs4597169	C/T
29109557	29109557	SG13S112	FLA295481			C/T
29109773	29109773	SG13S113	FLA295697		rs4293222	C/G
29110096	29110096	SG13S114	FLA296020	DG00AAHID		A/T
29110178	29110178	SG13S115	FLA296102			A/T
29110508	29110508	SG13S116	FLA296432		rs4769871	C/T
29110630	29110630	SG13S117	FLA296554		rs4769872	A/G
29110689	29110689	SG13S118	FLA296613		rs4769873	C/T
29110862	29110862	SG13S119	FLA296786			A/G
29111889	29111889	SG13S120	FLA297813			C/T
29112174	29112174	SG13S121	FLA298098	DG00AAHIJ	rs4503649	A/G
29112264	29112264	SG13S122	FLA298188	DG00AAHIH		A/G
29112306	29112306	SG13S123	FLA298230			C/T
29112455	29112455	SG13S43	FLA298379		rs3885907	A/C

29112583	29112583	SG13S399	FLA298507		A/C
29112680	29112680	SG13S124	FLA298604	rs3922435	C/T
29113139	29113139	SG13S125	FLA299063		A/G
29114056	29114056	SG13S400	FLA299980		A/G
29114738	29114738	SG13S126	FLA300662		A/G
29114940	29114940	SG13S127	FLA300864		A/G
29115878	29115878	SG13S128	FLA302094	rs4254165	A/G
29116020	29116020	SG13S129	FLA302236	rs4360791	A/G
29116068	29116068	SG13S130	FLA302284		G/T
29116196	29116296	EXON2			
29116249	29116249	SG13S190	FLA302465		C/T
29116308	29116308	SG13S192	FLA302524	B_SNP_302524	rs3803277 A/C
29116344	29116344	SG13S193	FLA302560		A/G
29116401	29116401	SG13S88	FLA302617	B_SNP_302617	rs3803278 C/T
29116688	29116688	SG13S131	FLA302904		C/T
29117133	29117133	SG13S132	FLA303349		A/C
29117546	29117546	SG13S133	FLA303762	rs4356336	C/T
29117553	29117553	SG13S38	FLA303769	rs4584668	A/T
29117580	29117580	SG13S134	FLA303796		C/T
29117741	29117741	SG13S135	FLA303957	rs4238137	C/T
29117954	29117954	SG13S136	FLA304170	rs4147063	C/T
29118118	29118118	SG13S137	FLA304334	DG00AAHIG	rs4147064 C/T
29118815	29118815	SG13S86	FLA305031		A/G
29118873	29118873	SG13S87	FLA305089	DG00AAHOJ	A/G
29119069	29119069	SG13S138	FLA305285		C/T
29119138	29119138	SG13S139	FLA305354		C/G
29119289	29119289	SG13S140	FLA305505		A/G/T
29119462	29119462	SG13S141	FLA305678		C/T
29119740	29119740	SG13S39	FLA305956		G/T
29120939	29120939	SG13S142	FLA307155	rs4387455	C/T
29120949	29120949	SG13S143	FLA307165	rs4254166	C/T
29121342	29121342	SG13S144	FLA307558	rs4075692	A/G
29121572	29121572	SG13S145	FLA307788		C/G
29121988	29121988	SG13S146	FLA308204		C/T
29122253	29122253	SG13S26	FLA308469		C/T
29122283	29122283	SG13S27	FLA308499		A/G
29122294	29122294	SG13S147	FLA308510		C/T
29122298	29122298	SG13S28	FLA308514		G/T
29122311	29122311	SG13S148	FLA308527		G/T
29123370	29123370	SG13S98	FLA309586		G/T
29123635	29123635	SG13S149	FLA309851		A/G
29123643	29123643	SG13S29	FLA309859		A/C
29124188	29124259	EXON3			
29124441	29124441	SG13S89	FLA310657	B_SNP_310657	rs4769874 A/G
29124906	29124906	SG13S96	FLA311122		rs4072653 A/G
29125032	29125032	SG13S150	FLA311248		C/G
29125521	29125521	SG13S401	FLA311737		C/T
29125822	29125822	SG13S151	FLA312038		C/T
29125840	29125840	SG13S30	FLA312056		G/T
29127301	29127301	SG13S31	FLA313550		C/T
29128080	29128162	EXON4			
29128284	29128284	SG13S152	FLA314500		C/G
29128316	29128316	SG13S402	FLA314532	rs4468448	C/T
29128798	29128798	SG13S403	FLA315014	rs4399410	A/G
29129016	29129016	SG13S153	FLA315232		A/T
29129139	29129139	SG13S97	FLA315355		A/G
29129154	29129154	SG13S154	FLA315370		C/T

29129395	29129395	SG13S40	FLA315611		G/T
29129915	29129915	SG13S155	FLA316131		rs4769875 A/G
29130192	29130192	SG13S156	FLA316408		A/C
29130256	29130256	SG13S157	FLA316472		A/G
29130299	29130299	SG13S158	FLA316515		A/C
29130353	29130353	SG13S159	FLA316569		G/T
29130391	29130391	SG13S160	FLA316607		C/T
29130547	29130547	SG13S32	FLA316763		A/C
29131280	29131280	SG13S161	FLA317496		A/G
29131403	29131403	SG13S162	FLA317619		A/G
29131404	29131404	SG13S163	FLA317620		C/T
29131431	29131431	SG13S164	FLA317647		rs4769058 C/T
29131517	29131517	SG13S165	FLA317733		A/T
29131528	29131528	SG13S166	FLA317744		rs4769059 C/T
29131599	29131599	SG13S167	FLA317815		rs4769876 A/G
29132003	29132003	SG13S168	FLA318219		A/C
29133753	29133753	SG13S33	FLA319969		G/T
29134045	29134045	SG13S41	FLA320261		A/G
29134177	29134177	SG13S169	FLA320393		A/G
29134379	29134379	SG13S404	FLA320595		rs4427651 G/T
29135558	29135558	SG13S170	FLA321774		rs3935645 C/T
29135640	29135640	SG13S171	FLA321856		rs3935644 A/G
29135750	29135750	SG13S172	FLA321966		A/G
29135809	29135809	SG13S173	FLA322025		A/T
29135877	29135877	SG13S42	FLA322093		rs4769060 A/G
29136080	29136556	EXON5			
29136290	29136290	SG13S194	FLA322506		C/T
29136462	29136462	SG13S195	FLA322678		rs1132340 A/G
29136797	29136797	SG13S174	FLA323013		A/G
29137100	29137100	SG13S34	FLA323316		G/T
29137150	29137150	SG13S175	FLA323366		A/G
29137607	29137607	SG13S176	FLA323823		A/G
29137651	29137651	SG13S177	FLA323867		C/T
29137905	29137905	SG13S178	FLA324121		C/G
29138117	29138117	SG13S35	FLA324333		A/G
29138375	29138375	SG13S179	FLA324591		A/G
29138385	29138385	SG13S180	FLA324601		C/T
29138633	29138633	SG13S181	FLA324849	DG00AAHIF	rs4420371 C/G
29139153	29139153	SG13S182	FLA325369		C/T
29139277	29139277	SG13S183	FLA325493		rs4466940 C/T
29139435	29139435	SG13S184	FLA325651	DG00AAHOI	rs4445746 A/G
29139971	29139971	SG13S185	FLA326187		A/G
29140441	29140441	SG13S405	FLA326657		A/G
29140649	29140649	SG13S91	FLA326865		A/G
29140695	29140695	SG13S186	FLA326911		rs4769877 A/T
29140703	29140703	SG13S187	FLA326919		A/G
29140805	29140805	SG13S188	FLA327021	DG00AAJFE	A/G
29141049	29141049	SG13S406	FLA327265		C/T
29142392	29142392	SG13S92	FLA328644		rs4429158 C/T
29142397	29142397	SG13S93	FLA328649		A/G
29142712	29142712	SG13S36	FLA328964		C/T
29144013	29144013	SG13S407	FLA330265		C/T
29144203	29144203	SG13S408	FLA330455		C/T
29144234	29144589	D13S1238			
29144255	29144255	SG13S7	FLA330507		C/T
29144877	29144877	SG13S37	FLA331129		A/G

29144982	29144982	SG13S409	FLA331234
29144983	29144983	SG13S8	FLA331235
29145122	29145122	SG13S410	FLA331374
29145143	29145143	SG13S411	FLA331395
29145171	29145171	SG13S9	FLA331423
29145221	29145221	SG13S412	FLA331473
29145265	29145265	SG13S413	FLA331517

	A/G
rs4491352	A/C
rs4319601	C/T
	A/G
	C/T
rs4769062	A/G
rs4238138	C/T

minor allele	minor allele frequenc y (%)	start position SEQ NO:1	end in position ID SEQ NO:1
G	10.32	432	432
G	30.46	28356	28356
T	37.38	33803	33803
G	0.545	42627	42627
G	1.111	43101	43101
G	0.328	43315	43315
C	0.495	43353	43353
A	6.993	43774	43774
C	30.876	53244	53244
G	6.731	53303	53303
T	0.353	53423	53423
C	31.356	53734	53734
A	30.935	53902	53902
G	5.492	71869	71869
A	1.812	72696	72696
G	35.00	75670	75670
C	1.314	83410	83410
T	3.521	93792	93792
A	30.031	94202	94202
A	1.724	94668	94668
A	0.369	106707	106707
A	13.66	110180	110180
A	20.779	117355	117355
T	5.965	117446	117446
A	16.923	118416	118416
A	34.364	127348	127348
A	8.537	127383	127383
T	25.536	127402	127402
		131702	131949
		132359	132753
A	37.302	134272	134272
C	6.25	138551	138551
A	0.49	149983	149983
A	14.08	150200	150200
G	0.62	150357	150357
G	14.01	151350	151350
T	0.58	151518	151518
C	30.21	153102	153102
A	10.95	153190	153190
G	30.00	154224	154224
A	27.95	155473	155473

G	2.41	156090	156090
A	0.39	156186	156186
T	10.23	156473	156473
T	15.17	157044	157044
T	13.60	157886	157886
G	12.44	158025	158025
A	13.45	158054	158054
G	14.59	158997	158997
T	26.84	159307	159307
A	12.73	159580	159580
C	43.67	159780	159780
A	12.18	160287	160287
A	8.38	160536	160536
G	0.62	160594	160594
T	12.34	160947	160947
G	25.34	161964	161964
C	0.24	162259	162259
T	25.66	162999	162999
A	14.84	164688	164688
G	12.37	164813	164813
C	14.55	164874	164874
G	11.99	164962	164962
C	14.66	165476	165476
A	12.21	165553	165553
A	0.79	166486	166486
C	10.15	166891	166891
C	3.53	166979	166979
A	12.45	169965	169965
C	0.62	171909	171909
G	31.55	172271	172271
G	4.94	172629	172629
C	15.51	172646	172646
T	27.91	173099	173099
G	14.74	174329	174329
T	1.17	174652	174652
T	1.28	175138	175138
A	2.17	175404	175404
		175668	175812
A	30.11	175830	175830
G	0.66	176398	176398
A	28.31	176579	176579
G	14.85	176919	176919
C	1.21	176972	176972
A	1.04	177112	177112
G	0.88	177182	177182
C	1.14	177344	177344
T	7.10	177557	177557
C	22.52	177773	177773
A	20.86	178096	178096
T	13.83	178178	178178
T	4.05	178508	178508
A	4.07	178630	178630
T	4.07	178689	178689
A	1.06	178862	178862

C	16.00	179889	179889
G	49.36	180174	180174
A	29.75	180264	180264
T	5.06	180306	180306
C	46.23	180455	180455
C	1.59	180583	180583
T	1.45	180680	180680
G	11.32	181139	181139
A	3.25	182056	182056
A	34.12	182738	182738
G	29.63	182940	182940
A	45.68	183878	183878
G	36.65	184020	184020
G	8.07	184068	184068
		184196	184296
T	1.02	184249	184249
A	49.57	184308	184308
A	0.58	184344	184344
C	24.71	184401	184401
T	7.19	184688	184688
A	1.10	185133	185133
T	37.65	185546	185546
A	45.50	185553	185553
T	1.22	185580	185580
T	0.89	185741	185741
T	36.69	185954	185954
T	29.11	186118	186118
A	30.19	186815	186815
G	3.29	186873	186873
T	36.96	187069	187069
G	36.63	187138	187138
T	37.34	187289	187289
C	1.15	187462	187462
T	9.91	187740	187740
C	3.36	188939	188939
T	36.24	188949	188949
A	31.58	189342	189342
G	0.45	189572	189572
T	1.14	189988	189988
T	46.57	190253	190253
A	10.34	190283	190283
T	8.00	190294	190294
T	33.71	190298	190298
T	2.29	190311	190311
G	1.19	191370	191370
A	1.01	191635	191635
A	47.88	191643	191643
		192188	192259
A	4.68	192441	192441
G	29.72	192906	192906
C	8.22	193032	193032
C	21.10	193521	193521
T	8.57	193822	193822
T	23.23	193840	193840
T	24.20	195301	195301
		196080	196162



C	23.89	196284	196284
T	19.33	196316	196316
G	11.50	196798	196798
T	3.08	197016	197016
A	9.72	197139	197139
T	0.98	197154	197154
T	2.24	197395	197395
A	1.43	197915	197915
A	1.80	198192	198192
G	2.38	198256	198256
A	0.61	198299	198299
G	2.55	198353	198353
T	0.83	198391	198391
C	48.50	198547	198547
G	2.44	199280	199280
G	2.45	199403	199403
C	2.45	199404	199404
C	2.55	199431	199431
T	20.00	199517	199517
T	2.46	199528	199528
A	3.50	199599	199599
C	8.39	200003	200003
T	8.99	201753	201753
G	5.41	202045	202045
G	4.12	202177	202177
G	38.33	202379	202379
C	32.77	203558	203558
G	48.03	203640	203640
G	1.67	203750	203750
A	0.68	203809	203809
G	42.44	203877	203877
		204080	204556
T	0.30	204290	204290
G	2.46	204462	204462
G	0.56	204797	204797
G	30.23	205100	205100
A	2.40	205150	205150
A	2.24	205607	205607
T	1.64	205651	205651
C	1.40	205905	205905
A	9.52	206117	206117
A	48.14	206375	206375
T	2.50	206385	206385
C	49.41	206633	206633
T	2.36	207153	207153
T	12.07	207277	207277
A	16.67	207435	207435
G	7.66	207971	207971
A	9.66	208441	208441
A	7.78	208649	208649
A	25.71	208695	208695
A	1.43	208703	208703
G	4.71	208805	208805
T	0.56	209049	209049
T	8.33	210392	210392

A	7.23	210397	210397
C	15.88	210712	210712
T	3.29	212013	212013
T	0.30	212203	212203
		212234	212589
T	16.28	212255	212255
G	16.70	212877	212877
A	1.93	212982	212982
C	30.64	212983	212983
T	20.57	213122	213122
A	1.54	213143	213143
C	16.37	213171	213171
A	7.42	213221	213221
T	1.91	213265	213265

Table 14: Extended 4 microsatellite marker haplotypes

4 markers :	pos.rr-frqgt1perc												
Length	p-val	RR	N_af	P_al	P_ca	N_ct	P_al	P_ca	Alleles				Markers
0.88	4.71E-06	6.23	428	0.065	0.125	721	0.011	0.022	0	-12	-6	0	DG13S80 DG13S83 DG13S1110 DG13S163
0.82	8.60E-06	INF	438	0.032	0.062	720	0	0	0	4	2	14	DG13S111 1 DG13S1103 D13S1287 DG13S1061
0.67	6.98E-06	19.91	435	0.03	0.059	721	0.002	0.003	8	6	0	8	DG13S1103 DG13S163 D13S290 DG13S1061
0.767	4.85E-06	26.72	436	0.048	0.094	721	0.002	0.004	0	0	2	12	DG13S1101 DG13S166 D13S1287 DG13S1061
0.515	1.93E-06	INF	422	0.048	0.094	721	0	0	2	0	0	6	DG13S166 DG13S163 D13S290 DG13S1061
0.864	1.68E-06	INF	424	0.024	0.048	717	0	0	0	2	0	-16	DG13S166 DG13S163 DG13S1061 DG13S293
0.927	5.38E-06	INF	435	0.034	0.067	720	0	0	4	2	14	3	DG13S1103 D13S1287 DG13S1061 DG13S301

Alleles #'s: For SNP alleles A = 0, C = 1, G = 2, T = 3; for microsatellite

alleles: the CEPH sample (Centre d'Etudes du Polymorphisme Humain, genomics repository) is used as a reference, as described above.

Length=length of haplotype in Mb. P-val=p-value. RR=Relative risk. N af=Number of patients. P al=allelic frequency of haplotype. P ca =carrier frequency of haplotype. N ct= number of controls. Alleles= alleles in the haplotype. Markers= markers in the haplotype.

**Table 15: Extended 5 microsatellite marker haplotypes**

[illegible]

																	D13S1287 DG13S1061
																	DG13S175 DG13S1103 DG13S163 D13S290 DG13S1061
0.705	5.28E-06	INF	435	0.027	0.053	721	0	0	0	8	6	0	8				DG13S89 DG13S166 DG13S163 D13S290 DG13S1061
0.841	4.21E-06	INF	422	0.048	0.093	721	0	0	0	2	0	0	6				DG13S1101 DG13S175 DG13S166 D13S1287 DG13S1061
0.767	4.02E-06	28.11	436	0.049	0.095	721	0.002	0.004	0	0	0	2	12				DG13S1101 DG13S172 DG13S166 D13S1287 DG13S1061
0.767	1.29E-06	31.07	436	0.047	0.092	721	0.002	0.003	0	0	0	2	12				DG13S175 DG13S166 DG13S163 D13S290 DG13S1061
0.705	4.25E-07	INF	422	0.048	0.093	721	0	0	0	2	0	0	6				DG13S172 DG13S1103 DG13S166 D13S1287 DG13S1061
0.683	6.58E-06	INF	437	0.029	0.056	721	0	0	0	4	0	2	14				DG13S1101 DG13S166 D13S290 D13S1287 DG13S1061
0.767	2.85E-06	32.43	436	0.044	0.087	721	0.001	0.003	0	0	0	2	12				D13S289 DG13S166 DG13S163 D13S1287 DG13S293
0.865	9.58E-06	18.39	451	0.023	0.045	739	0.001	0.003	0	0	2	2	16				D13S289 DG13S166 DG13S163 DG13S1061 DG13S293
0.865	5.08E-06	INF	453	0.019	0.038	739	0	0	0	0	2	0	16				DG13S1103 DG13S166 D13S1287 DG13S1061 DG13S301
0.927	1.02E-07	27.65	437	0.037	0.073	721	0.001	0.003	4	0	2	14	3				

Length=length of haplotype in Mb. P-val=p-value. RR=Relative risk. N af=Number of patients. P al=allelic frequency of haplotype. P ca =carrier frequency of haplotype. N ct= number of controls. Alleles= alleles in the haplotype. Markers= markers in the haplotype

## EXAMPLE 2: RELATIONSHIP BETWEEN POLYMORPHISM IN THE 5-LIPOXYGENASE PROMOTER AND MI

5           A family of mutations in the G-C rich transcription factor binding region of the 5-LO gene has previously been identified. These mutations consist of deletion of one, deletion of two, or addition of one zinc finger (Sp1/Egr-1) binding sites in the region 176 to 147 bp upstream from the ATG translation start site where there are normally 5 Sp1 binding motifs in tandem. These naturally occurring mutations in the human 5-LO  
10 gene promoter have been shown to modify transcription factor binding and reporter gene transcription. The capacity of the mutant forms of DNA to promote transcription of CAT reporter constructs have been shown to be significantly less than that of the wild type DNA (*J. Clin. Invest.* Volume 99, Number 5, March 1997, 1130-1137). To test whether 5-LO is associated with the atherosclerotic diseases, particularly myocardial  
15 infarction (MI) in the human population, this promoter polymorphism, consisting of variable number of tandem Sp1/Egr-1 binding sites, was genotyped in 1112 MI patients, 748 patients with PAOD, and 541 stroke patients.

The results, shown in Table 16, demonstrate that the wild type allele (which represents the allele with the most active promoter and thus with the highest expression of the 5-  
20 LO mRNA; *J. Clin. Invest.* Volume 99, Number 5, March 1997, 1130-1137) is significantly associated with MI (RR=1.2,  $p<0.05$ ). The results are consistent with a disease hypothesis that increased expression of the 5-LO plays a role in the pathogenesis of MI.

Table 16

	N_aff	Frq_aff	N_ctrl	Frq_ctrl	Risk Ratio	P-value
<b>MI patients</b>	1112	0.8701	734	0.8501	1.1803	0.048
Independent	969	0.8720	734	0.8501	1.2013	0.037
Males	646	0.8740	734	0.8501	1.2232	0.039
Females	465	0.8645	734	0.8501	1.1249	0.180
Age of onset < 60	522	0.8745	734	0.8501	1.2286	0.046
Males	353	0.8768	734	0.8501	1.2542	0.053
Females	169	0.8698	734	0.8501	1.1779	0.202
<b>PAOD patients</b>	748	0.8763	734	0.8501	1.2492	0.022
Independent	703	0.8755	734	0.8501	1.2400	0.027
Males	473	0.8774	734	0.8501	1.2613	0.033
Females	275	0.8745	734	0.8501	1.2289	0.092
<b>Stroke patients</b>	541	0.8743	734	0.8501	1.2262	0.046
Males	326	0.8758	734	0.8501	1.2427	0.067
Females	215	0.8721	734	0.8501	1.2019	0.144
Cardio / Large V	202	0.8861	734	0.8501	1.3719	0.038
Cardioembolic	114	0.8772	734	0.8501	1.2592	0.165
Large Vessel	88	0.8977	734	0.8501	1.5474	0.053
Small Vessel	77	0.8831	734	0.8501	1.2791	0.163
Hemorrhagic	27	0.9259	734	0.8501	2.2035	0.081

single sided p-values: Fisher exact test. N\_aff= number of affected individuals;

Frq\_aff= frequency of the wild type allele of the promoter polymorphism in the

affected group; N\_ctrl= number of controls; Frq\_ctrl= frequency of the wild type allele

5 of the promoter polymorphism in the control group;

### EXAMPLE 3: ELEVATED LTE4 BIOSYNTHESIS IN INDIVIDUALS WITH THE FLAP MI-RISK HAPLOTYPE

Based on the known function of the end products of the leukotriene pathway  
 10 and based on our 5-LO association data, the association of the FLAP haplotype with  
 MI is best explained by increased expression and/or increased function of the FLAP  
 gene. In other words, those individuals that have a “at risk” FLAP haplotype have  
 either, or both, increased amount of FLAP, or more active FLAP. This would lead to  
 increased production of leukotrienes in these individuals.

To demonstrate this theory, LTE4, a downstream leukotriene metabolite, was measured in patient serum samples. A quantitative determination of LTE4 in human serum was performed by liquid chromatography coupled with tandem mass spectrometry. The protocol was performed as follows:

5

ANALYTICAL METHOD

Table P1 (Protocol 1): List of Abbreviations

CAN	Acetonitrile
IS	Internal standard
LC-MS/MS	Liquid chromatography tandem mass spectrometry
LOQ	Limit of quantification
QCs	Quality controls
R <sup>2</sup>	Coefficient of determination
SS	Spiking solution

10



*Apparatus and conditions*

Table P2: Analytical apparatus and conditions

Instruments / Conditions	Details																												
Analytical column	Zorbax extend C <sub>18</sub> , 3.5µm (50 x 2.1 mm)																												
Column temperature	Ambient																												
Pump and flow	Hewlett Packard Series 1100 Binary pump delivering 0.3 ml/min																												
Mobile phase	A: Buffer: Acetonitrile:H <sub>2</sub> O (5:95 % v/v). (Containing 10 mM Ammonium Acetate and 0.1% Acetic acid at pH 4.6). B: Buffer: Acetonitrile:H <sub>2</sub> O (95:5 % v/v). (Containing 10 mM Ammonium Acetate and 0.1% Acetic acid at pH 4.6).																												
Gradient	<table><tr><td>Time</td><td>%A</td><td>%B</td><td>Flow rate</td></tr><tr><td>0.00</td><td>30</td><td>70</td><td>0.3 ml/min</td></tr><tr><td>1.00</td><td>30</td><td>70</td><td>0.3 ml/min</td></tr><tr><td>1.50</td><td>90</td><td>10</td><td>0.3 ml/min</td></tr><tr><td>6.00</td><td>90</td><td>10</td><td>0.3 ml/min</td></tr><tr><td>6.50</td><td>30</td><td>70</td><td>0.3 ml/min</td></tr><tr><td>10.00</td><td>30</td><td>70</td><td>0.3 ml/min</td></tr></table>	Time	%A	%B	Flow rate	0.00	30	70	0.3 ml/min	1.00	30	70	0.3 ml/min	1.50	90	10	0.3 ml/min	6.00	90	10	0.3 ml/min	6.50	30	70	0.3 ml/min	10.00	30	70	0.3 ml/min
Time	%A	%B	Flow rate																										
0.00	30	70	0.3 ml/min																										
1.00	30	70	0.3 ml/min																										
1.50	90	10	0.3 ml/min																										
6.00	90	10	0.3 ml/min																										
6.50	30	70	0.3 ml/min																										
10.00	30	70	0.3 ml/min																										
Sample injection	HTC PAL autosampler 10 µl onto the HPLC column																												
Mass Spectrometric system	Quattro Ultima <sup>TM</sup> Tandem MS/MS, Micromass. England.																												
Recording and integration	Mass Lynx, version 3.5. All chromatograms and reports are printed out in hardcopy and stored in electronic form on the workstation hard disk drive. Recording time was 10 min.																												
Retentions times	LTE <sub>4</sub> ~ 3.05 min. LTE <sub>4</sub> -d <sub>3</sub> ~ 3.05 min.																												
Ionization mode	Electrospray atmospheric pressure in negative ion mode																												
Scan mode	Multiple reaction monitoring (MRM)																												
	<table><tr><td>Compound</td><td>Parent ion</td><td>Daughter ion</td></tr></table>	Compound	Parent ion	Daughter ion																									
Compound	Parent ion	Daughter ion																											

	LTE <sub>4</sub>	438.2	333.2
	LTE <sub>4</sub> -d <sub>3</sub>	441.2	336.2

*Other instruments*

Table P3: The apparatus used for sample treatment and measurements

Apparatus	Brand	Type
Pipette	Eppendorf	Edos 5221
Pipette	Labsystems	Finnpipette 200 µl
Centrifuge	Eppendorf	5417C
Evaporation unit	Porvair	Ultravap
Vibrofix	Ika-Werk Thermolyne	VF-1 Maxi-mix III™, 65800
Balance	Sartorius	LA 120 S
Ultra sonic bath	Cole Parmer	8891

*Materials*

5 Table P4: Reagents for sample treatment and measurements

Reagent	Manufacturer	Quality	Art no.
Acetonitrile (ACN)	Rathburn	HPLC grade	RH 1016
Methanol	Rathburn	HPLC grade	RH 1019
Ammonium acetate	Merck	Pro analysis	1116

Table P5: Reference substances

	Details	Reference
Reference standards	Leukotrine E <sub>4</sub> from Cayman Chemical, MI, USA	20410
Internal standards	Leukotriene E <sub>4</sub> -20, 20,20-d <sub>3</sub> from Biomol, PA, USA	S10120

*Stock solutions*

A stock solution of LTE<sub>4</sub> was prepared by the supplier at a concentration of 100 µg/ml in methanol. The stock solution was diluted to a concentration of 20 µg/ml in methanol and this working solution (WS-1) was kept refrigerated at 2-8°C.

- 5 An internal standard stock solution (LTE<sub>4</sub>-d<sub>3</sub>) was prepared by the supplier at concentration of 49.5 µg/ml. The stock solution was diluted to a concentration of 1 µg/ml in methanol and this working solution was kept refrigerated at 2-8°C.

*Preparation of spiking solutions, calibration standards and quality control samples*

- Spiking solutions (SS) in the concentration range of 1 ng/ml to 10000 ng/ml  
10 were prepared by dilution of the working Solution.

The following spiking solutions were prepared:

Table P6: Spiking solutions for calibration standards

SS	Concentration (ng/ml)	Preparation
1	10000	500 µl of WS-1 (20 µg/ml) diluted to 1.0 ml with 70% MeOH/water
2	1000	100 µl of SS-1 was diluted to 1.0 ml with 70% MeOH/water
3	100	100 µl of SS-2 was diluted to 1.0 ml with 70% MeOH/water
4	30	300 µl of SS-3 was diluted to 1.0 ml with 70% MeOH/water
5	20	200 µl of SS-3 was diluted to 1.0 ml with 70% MeOH/water
6	16	160 µl of SS-3 was diluted to 1.0 ml with 70% MeOH/water
7	12	120 µl of SS-3 was diluted to 1.0 ml with 70% MeOH/water
8	8.0	400 µl of SS-5 was diluted to 1.0 ml with 70% MeOH/water
9	4.0	200 µl of SS-5 was diluted to 1.0 ml with 70% MeOH/water
10	2.0	100 µl of SS-5 was diluted to 1.0 ml with 70% MeOH/water
11	1.4	175 µl of SS-8 was diluted to 1.0 ml with 70% MeOH/water
12	1.0	125 µl of SS-8 was diluted to 1.0 ml with 70% MeOH/water

Table P7: Spiking solutions for quality controls

SS	Concentration (ng/ml)	Preparation
13	14	140µl of SS-3 was diluted to 1.0 ml with 70% MeOH/water
14	6.0	300µl of SS-5 was diluted to 1.0 ml with 70% MeOH/water
15	2.4	120µl of SS-5 was diluted to 1.0 ml with 70% MeOH/water

After preparation, spiking solutions for calibration standards and quality controls were kept refrigerated at 2-8°C.

5

*Preparation of calibration standards and quality controls*

Fresh calibration standards and quality controls (QCs) were prepared each day by spiking blank plasma as described in Tables P8 and P9, respectively.

10 Table P8: Preparation of calibration standards

Concentration (ng/ml)	SS (µl)	Blank Plasma
1500	20 µl of the SS-4 (30ng/ml)	380 µl
1000	20 µl of the SS-5 (20ng/ml)	380 µl
800	20 µl of the SS-6 (16ng/ml)	380 µl
600	20 µl of the SS-7 (12ng/ml)	380 µl
400	20 µl of the SS-8 (8ng/ml)	380 µl
200	20 µl of the SS-9 (4.0ng/ml)	380 µl
100	20 µl of the SS-10 (2.0ng/ml)	380 µl
70	20µl of the SS-11 (1.4ng/ml)	380 µl
50	20µl of the SS-12 (1.0ng/ml)	380 µl

Table P9: Preparation of quality controls

Concentration (ng/ml)	SS ( $\mu$ l)	Blank Plasma
800	20 $\mu$ l of the SS-13 (14ng/ml)	380 $\mu$ l
40	20 $\mu$ l of the SS-14 (6.0ng/ml)	380 $\mu$ l
8.0	20 $\mu$ l of the SS-15 (2.4ng/ml)	380 $\mu$ l

#### 5 *Sample preparation*

Aliquots of 400  $\mu$ l of each study sample, calibration standards, QC samples and control blank are pipetted into an eppendorf vial. All samples apart from blank are then spiked with 20  $\mu$ l of internal standard working solution and the samples are then vortex-mixed for few seconds. The pH of the plasma samples is adjusted to pH 4.5 using 60  $\mu$ l of 10% acetic acid and centrifuged for 10 min. at 4100 rpm immediately before the extraction. The solid phase extraction 96-well plate is conditioned with 1 ml methanol and 1 ml water. Then 400 $\mu$ l of the plasma samples are loaded on the plate. Vacuum is applied, followed by drying the disk for 1 min. After being washed with 2ml water and 1 ml 30% methanol in 2% acetic acid. Next the plate is eluted with 0.6 ml methanol. The plate is then dried for few minutes. The methanol eluate is evaporated almost to dryness under a stream of nitrogen at 45°C. The residue is reconstituted in 30  $\mu$ l mobile phase and vortex-mixed for few min. Subsequently, the solutions are centrifuged for 10 min at 10.000 rpm. and 10  $\mu$ l are injected by the autosampler into the LC-MS/MS system for quantification.

20

#### *PERFORMANCE OF MEASUREMENTS*

The samples will be prepared and measured in batches and a typical batch will consist of:

One set of calibration standards, one extra lowest calibration standard and one blank.

25 Samples collected from a 16 individuals and one set of control samples ( $C_L$ ,  $C_M$ ,  $C_H$ )

Samples collected from a 17 individuals and one set of control samples ( $C_L$ ,  $C_M$ ,  $C_H$ )

#### *QUANTITATIVE DETERMINATION OF ANALYTE IN PLASMA SAMPLES*

The standard curve is calculated from the peak area ratios

5 ANALYTE/INTERNAL STANDARD of the calibration standards and their nominal ANALYTE concentrations. The unknown samples for  $LTE_4$  were calculated from a quadratic regression equation where a weighted curve,  $1/X^2$ , is used. The measured peak area of the samples was converted into pictogram of ANALYTE per milliliter (pg/ml) of plasma according to the calculated equation for the standard curve.

10 The calculation of the regression for the standard curve and the calculations of the concentration of the unknown samples and the control samples are performed with MassLynx Software.

#### 15 *ACCEPTANCE CRITERIA*

##### *Calibration standards*

The coefficient of determination ( $R^2$ ) for the calibration curve must exceed 0.98.

The calibration curve included the concentration range from 50pg/ml –  
20 1500pg/ml.

Concentration of the calibration standards must be within  $\pm 25\%$  of their nominal value when recalculated from the regression equation. Calibration standards that fail these criteria (at most 3 in each run) are rejected and the calibration performed again with the remaining standards. If the standard curve is not accepted, the samples must be  
25 reanalyzed.

##### *Control samples*

At least two thirds of the analysed quality controls must be within  $\pm 25\%$  of their nominal value when calculated from regression equation. If more than a third of the controls fail, the samples must be reanalyzed.

Table 17 (below) shows that the female MI “at risk” haplotype was more associated with female MI patients who have high LTE4 levels (top 50th percentile), than with female MI patients who have low levels of LTE4 (bottom 50th percentile).

Note that LTE4 may simply reflect the leukotriene synthesis rate of the leukotriene synthetic pathway upstream of the key leukotriene metabolite involved in MI risk. For example, leukotriene B4 is probably more likely than leukotriene E4 to be involved in the inflammatory aspects of MI plaques but since B4 has a short half life, it is difficult to measure reliably in serum samples, while E4 has long term stability.

[illegible]

	C	T	O	T	T	G	-2	4.65E-02	185	0.040	809	0.015	2.67	0.048	0.511
	C	T	O			G	-22.88E-02	182	0.087	809	0.048	1.89	0.08	0.622	

**P-val:** p-value for the association. **N<sub>aff</sub>:** Number of patients used in the analysis. **Aff.frq:** haplotype frequency in patients. **N<sub>ctrl</sub>:** number of controls used in the analysis. **Ctrl.frq:** Haplotype frequency in controls. **Rel\_risk:** Relative risk of the haplotype. **PAR:** population attributable risk. **Info:** information content. Less association was found between the at risk haplotype for female MI, with female MI who also have low levels of LTE4 (<50pg/ml).

10

Table 18: Association between haplotypes that were most significantly associated with female MI, and serum LTE4 levels.

	SG13S418	SG13S420	DG13S166	SG13S114	SG13S88	SG13S184	D13S1238	p-val	N <sub>aff</sub>	aff.frq	N <sub>ctrl</sub>	ctrl.frq	rel_risk	PAR	info
High vs low LTE4															
	C	T	O	T	T	G	-2	1.61E-01	221	0.084	185	0.054	1.61	0.063	0.689
	C	T	O			G	-2	1.20E-01	220	0.13	182	0.088	1.54	0.089	0.686

**P-val:** p-value for the association. **N<sub>aff</sub>:** Number of patients used in the analysis. **Aff.frq:** haplotype frequency in patients. **N<sub>ctrl</sub>:** number of controls used in the analysis. **Ctrl.frq:** Haplotype frequency in controls. **Rel\_risk:** Relative risk of the haplotype. **PAR:** population attributable risk. **Info:** information content. Here, the group of affected individuals were defined as female MI patients with high serum LTE4 (higher than 50 pg/ml) and the control group is defined as female MI patients with low serum LTE4 (below 50 pg/ml).

#### EXAMPLE 4: ELEVATED LTE4 CORRELATED WITH ELEVATED C-REACTIVE PROTEIN (CRP)

The relationship between the increased production of leukotrienes and the inflammatory marker CRP, a well established risk factor for MI, was then explored.

As shown in FIG. 5, a significant positive correlation was found between serum LTE4 levels and serum CRP levels.



EXAMPLE 5: ASSESSMENT OF LEVEL OF CRP IN PATIENTS WITH AT-RISK HAPLOTYPE

The level of CRP in female patients with female MI at-risk haplotypes was assessed, in order to assess whether there was a presence of a raised level of inflammatory marker in the presence of the female MI at-risk haplotype. Results are shown in Table 19. Although the association did not rise to the level of statistical significance, it was demonstrated that the average CRP was elevated in those patients with the at-risk haplotype versus those without it.

10

Table 19:  
All female  
patients

		no	Mean CRP	SE CRP
affecteds:	With haplotype.	155	4.91	8.7
	Not with haplotype.	218	4.35	6.13

EXAMPLE 6: ELEVATED SERUM LTE4 LEVELS IN MI PATIENTS VERSUS CONTROLS

The end products of the leukotriene pathway are potent inflammatory lipid mediators that can potentially contribute to development of atherosclerosis and destabilization of atherosclerotic plaques through lipid oxidation and/or proinflammatory effects. Examples one through five show that: 1) MI correlates with genetic variation at FLAP; 2) MI correlates with high expression promoter polymorphism at 5-LO; 3) C-reactive protein levels correlate with serum leukotriene E4; and 4) Patients with MI-risk FLAP haplotypes have higher levels of serum leukotriene E4 and CRP. Based on these data, it was hypothesized that serum leukotriene E4 levels correlate with MI risk.

To test this hypothesis, LTE4, a downstream leukotriene metabolite, was measured in 488 female MI patient and 164 control serum samples. The LTE4 levels for the patients were higher than that for the controls using a one-sided Wilcoxon rank-sum test. The p-value of the difference was 0.0092, thus confirming our hypothesis. Therefore, elevated leukotriene E4 represents a risk factor for MI. Serum or plasma

LTE4 levels may be used to profile the MI risk for individuals to aid in deciding which treatment and lifestyle management plan is best for primary or secondary MI prevention. In the same way other leukotriene metabolites may be used to risk profile for MI.

5

#### EXAMPLE 7: INCREASED LTB4 PRODUCTION IN ACTIVATED NEUTROPHILS FROM MI PATIENTS

A principal bioactive product of one of the two branches of the 5-LO pathway is  
10 LTB4. To determine whether the patients with past history of MI have increased activity of the 5-LO pathway compared to controls, the LTB4 production in isolated blood neutrophils was measured before and after stimulation *in vitro* with the calcium ionophore, ionomycin. No difference was detected between the LTB4 production in resting neutrophils from MI patients or controls (results not shown). In contrast, the  
15 LTB4 generation by neutrophils from MI patients stimulated with the ionophore was significantly greater than by neutrophils from controls at 15 and 30 minutes, respectively (FIG. 7.1). Moreover, as shown in FIG. 7.2, the observed increase in the LTB4 release was largely accounted for by male carriers of haplotype A4, whose cells produced significantly more LTB4 than cells from controls (P value =0.0042) (Table  
20 20). As shown in Table 20, there was also a heightened LTB4 response in males who do not carry HapA but of borderline significance. This could be explained by additional variants in the FLAP gene that have not been uncovered, or alternatively in other genes belonging to the 5-LO pathway, that may account for upregulation in the LTB4 response in some of the patients without the FLAP at-risk haplotype. As shown  
25 in Table 20, differences in LTB4 response were not detected in females. However, due to a small sample size this cannot be considered conclusive. Taken together, the elevated levels of LTB4 production of stimulated neutrophils from male carriers of the at-risk haplotype suggest that the disease associated variants in the FLAP gene increase FLAP's response to factors that stimulate inflammatory cells, resulting in increased  
30 leukotriene production and increased risk for MI.

## Methods

### *Isolation and activation of peripheral blood neutrophils*

50ml of blood were drawn into EDTA containing vacutainers from 43 MI patients and 35 age and sex matched controls. All blood was drawn at the same time in the  
5 early morning after 12 hours of fasting. The neutrophils were isolated using Ficoll-Paque PLUS (Amersham Biosciences).

Briefly, the red cell pellets from the Ficoll gradient were harvested and red blood cells subsequently lysed in 0.165 M  $\text{NH}_4\text{Cl}$  for 10 minutes on ice. After washing with PBS, neutrophils were counted and plated at  $2 \times 10^6$  cells/ml in 4ml cultures of 15%  
10 Fetal calf serum (FCS) (GIBCO BRL) in RPMI-1640 (GIBCO BRL). The cells were then stimulated with maximum effective concentration of ionomycin ( $1 \mu\text{M}$ ). At 0, 15, 30, 60 minutes post ionomycin addition 600 $\mu\text{l}$  of culture medium was aspirated and stored at  $-80^\circ\text{C}$  for the measurement of  $\text{LTB}_4$  release as described below. The cells  
15 were treated with indomethasine ( $1 \mu\text{M}$ ) to block the cyclooxygenase enzyme.

### *Ionomycin-induced release of $\text{LTB}_4$ in neutrophils*

$\text{LTB}_4$  Immunoassay (R&D systems) was used to quantitate  $\text{LTB}_4$  concentration in supernatant from cultured ionomycin stimulated neutrophils. The assay used is  
20 based on the competitive binding technique in which  $\text{LTB}_4$  present in the testing samples (200  $\mu\text{l}$ ) competes with a fixed amount of alkaline phosphatase-labelled  $\text{LTB}_4$  for sites on a rabbit polyclonal antibody. During the incubation, the polyclonal Ab becomes bound to a goat anti-rabbit Ab coated onto the microplates. Following a wash to remove excess conjugate and unbound sample, a substrate solution is added to the  
25 wells to determine the bound enzyme activity. The color development is stopped and the absorbance is read at 405 nm. The intensity of the color is inversely proportional to the concentration of  $\text{LTB}_4$  in the sample. Each  $\text{LTB}_4$  measurement using the  $\text{LTB}_4$  Immunoassay, was done in duplicate.

Table 20: LTB4 levels after ionomycin stimulation of isolated neutrophils<sup>a</sup>

Phenotype (n)	After 15 Minutes		After 30 Minutes	
	Mean (SD)	P value	Mean (SD)	P value
Controls (35)	4.53 (1.00)		4.67 (0.88)	
Males (18)	4.61 (1.10)		4.68 (1.07)	
Females (17)	4.51 (0.88)		4.67 (0.62)	
MI (41)	5.18 (1.09)	0.011	5.24 (1.06)	0.016
Carriers(16)	5.26 (1.09)	0.027	5.27 (1.09)	0.051
Non-carriers (24)	5.12 (1.08)	0.040	5.22 (1.03)	0.035
MI males (28)	5.37 (1.10)	0.0033	5.38 (1.09)	0.0076
Carriers(10)	5.66 (1.04)	0.0042	5.58 (1.12)	0.013
Non-carriers (18)	5.20 (1.09)	0.039	5.26 (1.05)	0.041
MI females (13)	4.78 (0.95)	0.46	4.95 (0.92)	0.36
Carriers(6)	4.59 (0.80)	0.90	4.75 (0.82)	0.85
Non-carriers (7)	4.94 (1.04)	0.34	5.12 (0.96)	0.25

<sup>a</sup>Mean  $\pm$  SD of log-transformed values of LTB4 levels of ionomycin-stimulated neutrophils from MI patients and controls. Results are shown for two time points: 15 and 30 minutes. The results for males and females and for MI male and female carriers and non-carriers of the at-risk haplotype HapA are shown separately. Two-sided p values corresponding to a standard two-sample test of the difference in the mean values between the MI patients, their various sub-cohorts and the controls are shown.

#### EXAMPLE 8: HAPLOTYPES ASSOCIATED WITH MI ALSO CONFER RISK OF STROKE AND PAOD.

Because stroke and PAOD are diseases that are closely related to MI (all occur on the basis of atherosclerosis), it was examined whether the SNP haplotype in the FLAP gene that confers risk to MI also conferred risk of stroke and/or PAOD. The 'at risk' haplotype (A4 haplotype) can be defined by the following 4 SNPs: SG13S25 with allele G, SG13S114 with allele T, SG13S89 with allele G, and SG13S32 with allele A.

Table 21 shows that the haplotype A4 increases the risk of having a stroke to a similar extent as it increases the risk of having an MI. The 'at risk' haplotype is carried by 28% of stroke patients and 17% of controls, meaning that the relative risk of having stroke for the carriers of this haplotype is 1.7 (p-value =  $5.8 \times 10^{-6}$ ). Although not as significant, the 'at risk' haplotype also confers risk of having PAOD.

Table 21:

		p-val	r	#aff	aff.frq.	#con	con.frq.	Info	SG13S25	SG13S106	SG13S114	SG13S89	SG13S30	SG13S32	SG13S42
<b>MI haplotypes</b>															
<b>All MI patients</b>															
	A4	5.3E-07	1.80	1407	0.16	614	0.09	0.82	G		T	G		A	
	B4	1.0E-04	1.87	1388	0.10	612	0.06	0.67	G	G			G		A
<b>Males MI</b>															
	A4	2.5E-08	2.00	864	0.17	614	0.09	0.82	G		T	G		A	
	B4	1.1E-05	2.12	852	0.11	612	0.06	0.67	G	G			G		A
<b>Females MI</b>															
	A4	1.9E-02	1.44	543	0.13	614	0.09	0.73	G		T	G		A	
	B4	7.9E-02	1.45	536	0.08	612	0.06	0.60	G	G			G		A
<b>Replication in stroke</b>															
<b>All stroke patients</b>															
	A4	5.8E-06	1.73	1238	0.15	614	0.09	0.80	G		T	G		A	
	B4	2.3E-04	1.83	1000	0.10	612	0.06	0.71	G	G			G		A
<b>Males stroke</b>															
	A4	1.1E-06	1.91	710	0.17	614	0.09	0.79	G		T	G		A	
	B4	3.1E-05	2.11	574	0.11	612	0.06	0.72	G	G			G		A
<b>Females stroke</b>															
	A4	9.9E-03	1.49	528	0.13	614	0.10	0.74	G		T	G		A	
	B4	6.3E-02	1.47	426	0.08	612	0.06	0.70	G	G			G		A
<b>All stroke excluding MI</b>															
		8.4E-05	1.65	1054	0.15	614	0.09	0.78	G		T	G		A	
<b>Males stroke excluding MI</b>															
		6.4E-05	1.78	573	0.16	614	0.09	0.75	G		T	G		A	
<b>Females stroke excluding MI</b>															
		1.2E-02	1.49	481	0.14	614	0.10	0.72	G		T	G		A	
<b>Cardioembolic stroke</b>															
		6.6E-04	1.87	248	0.16	614	0.10	0.74	G		T	G		A	

Cardioembolic stroke excluding MI	3.8E-02	1.56	191	0.14	614	0.10	0.70	G		T	G	A
Large vessel stroke	8.0E-02	1.47	150	0.13	614	0.09	0.83	G		T	G	A
Large vessel stroke excluding MI	2.9E-01	1.31	114	0.12	614	0.09	0.80	G		T	G	A
Small vessel stroke	7.2E-04	2.05	166	0.18	614	0.09	0.71	G		T	G	A
Small vessel stroke excluding MI	1.0E-04	2.31	152	0.20	614	0.10	0.71	G		T	G	A
Hemorrhagic stroke	4.4E-02	1.73	97	0.15	614	0.09	0.72	G		T	G	A
Hemorrhagic stroke excluding MI	3.9E-02	1.78	92	0.16	614	0.09	0.71	G		T	G	A
Unknown cause stroke	1.3E-04	1.88	335	0.16	614	0.09	0.75	G		T	G	A
Unknown cause stroke excluding MI	6.5E-04	1.82	297	0.16	614	0.09	0.72	G		T	G	A
<b>MI and stroke together</b>												
All patients												
Best haplo A4	4.1E-07	1.75	2659	0.15	614	0.09	0.82	G		T	G	A
B4	4.1E-05	1.85	2205	0.10	612	0.06	0.70	G	G		G	A
Males												
A4	1.4E-08	1.93	1437	0.17	614	0.09	0.82	G		T	G	A
B4	2.0E-06	2.11	1290	0.11	612	0.06	0.70	G	G		G	A
Females												
A4	3.6E-03	1.47	1024	0.13	614	0.09	0.77	G		T	G	A
B4	2.8E-02	1.48	915	0.08	612	0.06	0.66	G	G		G	A
Patients with both MI and stroke												
A4	6.1E-05	2.10	184	0.18	614	0.09	0.86	G		T	G	A
<b>Replication in PAOD</b>												
All PAOD patients	3.6E-02	1.31	920	0.12	614	0.10	0.84	G		T	G	A
Males PAOD	1.8E-02	1.40	580	0.13	614	0.10	0.84	G		T	G	A
Females PAOD	3.7E-01	1.17	340	0.11	614	0.10	0.83	G		T	G	A
All PAOD excluding MI	1.1E-01	1.24	750	0.12	614	0.10	0.83	G		T	G	A
Males PAOD excluding MI	8.3E-02	1.30	461	0.12	614	0.10	0.83	G		T	G	A
Males PAOD excluding MI and stroke	8.7E-02	1.32	388	0.12	614	0.10	0.83	G		T	G	A

The patient cohorts used in the association analysis shown in Table 21 may include first and second degree relatives.

Table 21, discussed above, shows the results of the haplotype A4 association study using 779 MI patients, 702 stroke patients, 577 PAOD patients and 628

controls. First and second degree relatives were excluded from the patient cohorts. All known cases of MI were removed from the stroke and PAOD cohorts before testing for association. A significant association of the A4 haplotype to stroke was observed, with a relative risk of 1.67 (P value = 0.000095). In addition, it was  
 5 determined whether the A4 haplotype was primarily associated with a particular sub-phenotype of stroke, and found that both ischemic and hemorrhagic stroke were significantly associated with the A4 haplotype (Table 22).

Table 22: Association of the A4 haplotype to subgroups of stroke

Phenotype (n)	Pat. Frq.	RR	PAR	P-value
Stroke <sup>a</sup> (702)	0.149	1.67	0.116	0.000095
Ischemic (484)	0.148	1.65	0.113	0.00053
TIA (148)	0.137	1.51	0.090	0.058
Hemorrhagic (68)	0.167	1.91	0.153	0.024

<sup>a</sup>Excluding known cases of MI.

Finally, the A4 haplotype was less significantly associated with PAOD (Table 21). It should be noted that similar to the stronger association of the A4 haplotype to male MI compared to female MI, it also shows stronger association to male stroke and PAOD (Table 21).

#### Study population

The stroke and PAOD cohorts used in this study have previously been described (Gretarsdottir, S. *et al. Nat Genet* **35**, 131-8 (2003); Gretarsdottir, S. *et al., Am J Hum Genet* **70**, 593-603 (2002); Gudmundsson, G. *et al., Am J Hum Genet* **70**, 586-92 (2002)). For the stroke linkage analysis, genotypes from 342 male patients with ischemic stroke or TIA that were linked to at least one other male patient within and including 6 meioses in 164 families were used. For the association studies 702 patients with all forms of stroke (n=329 females and n=373 males) and 577 PAOD patients (n=221 females and n=356 males) were analysed. Patients with stroke or PAOD that also had MI were excluded. Controls used for the stroke and PAOD association studies were the same as used in the MI SNP association study (n=628).

The study was approved by the Data Protection Commission of Iceland and the National Bioethics Committee of Iceland. Informed consent was obtained from all study participants. Personal identifiers associated with medical information and blood samples were encrypted with a third party encryption system as previously described (Gulcher, J.R., Kristjansson, K., Gudbjartsson, H. & Stefansson, K., *Eur J Hum Genet* **8**, 739-42 (2000)).



In addition, in an independent linkage study of male patients with ischemic stroke or transient ischemic attack, linkage to the same locus was observed with a LOD score of 1.51 at the same peak marker (FIG. 10), further suggested that a cardiovascular susceptibility factor might reside at this locus.

5

#### EXAMPLE 9: HAPLOTYPE ASSOCIATION TO FLAP IN A BRITISH COHORT

In an independent study, it was determined whether variants in the FLAP gene also have impact on risk of MI in a population outside Iceland. The four SNPs, defining the A4 haplotype, were typed in a cohort of 750 patients from the United Kingdom who had sporadic MI, and in 728 British population controls. The patients and controls come from 3 separate study cohorts recruited in Leicester and Sheffield. No significant differences were found in the frequency of the haplotype between patients and controls (16.9% versus 15.3%, respectively). However, when an additional 9 SNPs, distributed across the FLAP gene, were typed in the British cohort and searched for other haplotypes that might be associated with MI, two SNPs showed association to MI with a nominally significant P value (data not shown). Moreover, three and four SNP haplotype combinations increased the risk of MI in the British cohort further and the most significant association was observed for a four SNP haplotype with a nominal P value = 0.00037 (Table 23).

20

**Table 23 Association of the HapB haplotype to British MI patients**

Phenotype (n)	Frq. Pat.	RR	PAR	P-value	P-value <sup>a</sup>
MI (750)	0.075	1.95	0.072	0.00037	0.046
Males (546)	0.075	1.97	0.072	0.00093	ND
Females (204)	0.073	1.90	0.068	0.021	ND

<sup>a</sup>P value adjusted for the number of haplotypes tested using 1,000 randomization tests.

Shown are the results for HapB that shows the strongest association in British MI cohort. HapB is defined by the following SNPs: SG13S377, SG13S114, SG13S41 and SG13S35 ( that have the following alleles A, A, A and G, respectively. In all three phenotypes shown the same set of n=728 British controls is used and the frequency of HapB in the control cohort is 0.040. Number of patients (n), haplotype frequency in patients (Frq. pat.), relative risk (RR) and population attributed risk (PAR).

This was called haplotype HapB. The haplotype frequency of HapB is 7.5% in the MI patient cohort (carrier frequency 14.4%), compared to 4.0% (carrier frequency 7.8%) in controls, conferring a relative risk of 1.95 (Table 23). This haplotype remained significant after adjusting for all haplotypes tested, using 1000 randomisation steps, with an adjusted P value = 0.046. No other SNP haplotype had an adjusted P value less than 0.05. The two at-risk haplotypes A4 and HapB appear to be mutually exclusive with no instance where the same chromosome carries both haplotypes.

#### *British study population*

The method of recruitment of 3 separate cohorts of British subjects has been described previously (Steeds, R., Adams, M., Smith, P., Channer, K. & Samani, N.J., *Thromb Haemost* **79**, 980-4 (1998); Brouillette, S., Singh, R.K., Thompson, J.R., Goodall, A.H. & Samani, N.J., *Arterioscler Thromb Vasc Biol* **23**, 842-6 (2003)). In brief, in the first two cohorts a total of 547 patients included those who were admitted to the coronary care units (CCU) of the Leicester Royal Infirmary, Leicester (July 1993–April 1994) and the Royal Hallamshire Hospital, Sheffield (November 1995–March 1997) and satisfied the World Health Organisation criteria for acute MI in terms of symptoms, elevations in cardiac enzymes or electrocardiographic changes (Nomenclature and criteria for diagnosis of ischemic heart disease. Report of the Joint International Society and Federation of Cardiology/World Health Organization task force on standardization of clinical nomenclature. *Circulation* **59**, 607-9 (1979)). A total of 530 control subjects were recruited in each hospital from adult visitors to patients with non-cardiovascular disease on general medical, surgical, orthopaedic and obstetric wards to provide subjects likely to be representative of the source population from which the subjects originated. Subjects who reported a history of coronary heart disease were excluded.

In the third cohort, 203 subjects were recruited retrospectively from the registries of 3 coronary care units in Leicester. All had suffered an MI according to WHO criteria before the age of 50 years. At the time of participation, patients were at

least 3 months from the acute event. The control cohort comprised 180 subjects with no personal or family history of premature coronary heart disease, matched for age, sex, and current smoking status with the cases. Control subjects were recruited from 3 primary care practices located within the same geographical area. In all cohorts  
5 subjects were white of Northern European origin.

#### DISCUSSION:

These results show that variants of the gene encoding FLAP associate with increased risk of MI and stroke. In the Icelandic cohort, a haplotype that spans the  
10 FLAP gene is carried by 30% of all MI patients and almost doubles the risk of MI. These findings were subsequently replicated in an independent cohort of stroke patients. In addition, another haplotype that spans the FLAP gene is associated with MI in a British cohort. Suggestive linkage to chromosome 13q12-13 was observed with several different phenotypes, including female MI, early onset MI of both sexes,  
15 and ischemic stroke or TIA in males. However, surprisingly, the strongest haplotype association was observed to males with MI or stroke. Therefore, there may be other variants or haplotypes within the FLAP gene, or in other genes within the linkage region, that also may confer risk to these cardiovascular phenotypes.

These data also show that the at-risk haplotype of the FLAP gene has  
20 increased frequency in all subgroups of stroke, including ischemic, TIA, and hemorrhagic stroke. Of interest is that the A4 haplotype confers significantly higher risk of MI and stroke than it does of PAOD. This could be explained by differences in the pathogenesis of these diseases. Unlike PAOD patients who have ischemic legs because of atherosclerotic lesions that are responsible for gradually diminishing blood  
25 flow to the legs, the MI and stroke patients have suffered acute events, with disruption of the vessel wall suddenly decreasing blood flow to regions of the heart and the brain.

Association was not found between the A4 haplotype and MI in a British cohort. However, significant association to MI was found with a different variant  
30 spanning the FLAP gene. The fact that different haplotypes of the gene are found conferring risk to MI in a second population is not surprising. A common disease like

MI associates with many different mutations or sequence variations, and the frequencies of these disease associated variants may differ between populations. Furthermore, the same mutations may be seen arising on different haplotypic backgrounds.

5

#### SUMMARY

In summary, it has been found that: MI correlates with genetic variation at FLAP; MI correlates with high expression promoter polymorphism at 5-LO; patients  
10 with female MI at-risk FLAP haplotypes have higher levels of serum LTE<sub>4</sub>; LTE<sub>4</sub> levels correlate with CRP levels in serum; and patients with MI at-risk FLAP haplotypes have elevated CRP. In addition, we have shown that isolated neutrophils from MI patients, produce more LTB<sub>4</sub> when stimulated with ionomycin compared to controls. Taken together, these results show that increased leukotriene synthesis is a  
15 risk factor for MI, and that this risk is driven in part by variants in FLAP and 5-LO genes and are captured in part by measurement of levels of serum LTE<sub>4</sub> and CRP. Furthermore, the SNP haplotype in the FLAP gene that confers risk to MI also confers risk of stroke and/or PAOD.

## MARKERS UTILIZED HEREIN

5 Table 24: Basepair position of microsatellite markers (start and stop of the amplicers in NCBI sequence assembly build 34 and primer sequences (forward and reverse)).

Marker name	forward primer	reverse primer	basepair start position	basepair stop position
DG13S2393	CCTTTGCTTTGTTCTATTTCCTT (SEQ ID NO. 4)	TCCCATGCCCAGAGTTAAT (SEQ ID NO. 5)	22831401	22831787
DG13S2070	TCCTCATGTCTTCACCTAGAAGC (SEQ ID NO. 6)	CCACTCATGAGGGAGCTGTT (SEQ ID NO. 7)	23020439	23020651
DG13S2071	TGTCACAGGCACACACTCTCT (SEQ ID NO. 8)	GAGTATGGCTGCTGCTCCTC (SEQ ID NO. 9)	23066973	23067076
DG13S2072	ATGGCTCACACTGGCCTAAA (SEQ ID NO. 10)	TGAACAGACCAATAATAGTGCAG (SEQ ID NO. 11)	23136964	23137114
DG13S2078	AAGCCACCCTTTAAACAGCA (SEQ ID NO. 12)	GCTGAGGAAGCAACTCCACT (SEQ ID NO. 13)	23591927	23592081
DG13S2079	GCTCTGAATTCCCTGGCATA (SEQ ID NO. 14)	TTAGCCCTAGTCCCCTCTCC (SEQ ID NO. 15)	23646974	23647183
DG13S2082	CAAGAGGCCTGCATAAGGAA (SEQ ID NO. 16)	AGATTGCCGGTGGCTTAAAT (SEQ ID NO. 17)	23807898	23808174
DG13S2083	TGTCTGTTCCCGTCTGTCTG (SEQ ID NO. 18)	TTATCCTCTGCCAAATTCC (SEQ ID NO. 19)	23882291	23882532
DG13S2086	GGCATGTATTCACTGCCTGA (SEQ ID NO. 20)	AAACCCATTCTTCTCTCTTAC (SEQ ID NO. 21)	24069346	24069771
DG13S2089	TATGTGTTCCAGCCAGACCTC (SEQ ID NO. 22)	CCCTGCCATGTGCATTAC (SEQ ID NO. 23)	24274920	24275129
DG13S44	CATTTCGGAAGGCAAAGAAA (SEQ ID NO. 24)	TTGCAATGAGGAATGAAGCA (SEQ ID NO. 25)	24413148	24413382
DG13S2095	TCCATTATCCATCTGTTCATTCA (SEQ ID NO. 26)	GAAGAATTAATTGTAGGAGGCA (SEQ ID NO. 27)	24621830	24622121
DG13S46	CTGACATCACCATGATCG (SEQ ID NO. 28)	CATACACAGCCATGTGGAATTA (SEQ ID NO. 29)	24652046	24652291
DG13S2101	ACGGTGATGACGCCTACATT (SEQ ID NO. 30)	TCACATGGACCAATTACCTAGAA (SEQ ID NO. 31)	24863557	24863744
D13S1254	AAATTACTTCATCTTGACGATAA (SEQ ID NO. 32)	CTATTGGGGACTGCAGAGAG (SEQ ID NO. 33)	25316434	25316657
DG13S55	AGCCAGTGTCACAAGGAAG (SEQ ID NO. 34)	GAGGGTGAGACACATCTCTGG (SEQ ID NO. 35)	25337471	25337753
DG13S54	AATCGTGCCTCAGTTCCATC (SEQ ID NO. 36)	CCACCAGGAACAACACACAC (SEQ ID NO. 37)	25377308	25377463
D13S625	TTGCTCTCCAGCCTGGGC (SEQ ID NO. 38)	TTCTCTGGCTGCCTGCG (SEQ ID NO. 39)	25391207	25391395
DG13S2695	TCCTGCATGAGAAGGAAGT (SEQ ID NO. 40)	CGACATTCAGTGGCTCTT (SEQ ID NO. 41)	25415551	25415807
DG13S1479	TTTGATTCCGTGGTCCATTA (SEQ ID NO. 42)	TTATTGGTGGTGCACCTTT (SEQ ID NO. 43)	25459039	25459368
DG13S2696	GGTGCACCGACAAATAAGT (SEQ ID NO. 44)	CCAGCTTATTCTCTGCCTTC (SEQ ID NO. 45)	25459351	25459478
DG13S1440	GGTAGGTTGAAATGGGCTAACA (SEQ ID NO. 46)	TCATGACAAGGTGTTGGATT (SEQ ID NO. 47)	25520858	25520987
DG13S1890	CCTCCTCTGCCATGAAGCTA (SEQ ID NO. 48)	CTATTGGTCTGCGGGTTGT (SEQ ID NO. 49)	25672727	25673140
DG13S1540	TACTGGGTTATCGCTGACC (SEQ ID NO. 50)	CCAATGGACCTCTTGACAT (SEQ ID NO. 51)	25704358	25704504
DG13S59	TTTCGGCACAGTCCTCAATA (SEQ ID NO. 52)	CAGCTGGGTGTGGTGACAT (SEQ ID NO. 53)	25720194	25720421
DG13S1545	CAGAGAGGAACAGGCAGAGG (SEQ ID NO. 54)	AGTGGCTGGGAAGCCTTATT (SEQ ID NO. 55)	25760018	25760404
DG13S1524	AGGTGAGAGAACAACCTGTCTT (SEQ ID NO. 56)	GCCTTCCTTCTAAGGCCAAC (SEQ ID NO. 57)	25843657	25843768

DG13S1529	CTGTAGACTTTATCCCTGACTTAC TG (SEQ ID NO. 58)	CAATGAATGATGAAGATTCCACT C (SEQ ID NO. 59)	26098943	26099063
DG13S1908	TGACACCATGTCTTACTGTTTGC (SEQ ID NO. 60)	GAGGATACAATGAGAACCAAATC TC (SEQ ID NO. 61)	26110282	26110493
DG13S2525	CAGGATCATCAGCCAGGTTT (SEQ ID NO. 62)	GCTGCATGTCTACTAGGCATT (SEQ ID NO. 63)	26123233	26123381
DG13S1546	CCACAGAATGCTCCAAAGGT (SEQ ID NO. 64)	GAGTCAAGTGATGGATGACGA (SEQ ID NO. 65)	26159644	26159995
DG13S1444	CAGATAGATGAATAGGTGGATGG A (SEQ ID NO. 66)	CACTGTTCCAAGTGCTTTGC (SEQ ID NO. 67)	26207544	26207727
DG13S66	TATGCGTTGTGTGTGCTGTG (SEQ ID NO. 68)	GGGCTTAGATTCTTGTAGTGG (SEQ ID NO. 69)	26279746	26279962
DG13S1907	TGTCCAGACTGCCTCCTACA (SEQ ID NO. 70)	TGCAACACCTGGTTCACAAT (SEQ ID NO. 71)	26378401	26378521
DG13S68	TTTGCAGTCCCTGTGGAGT (SEQ ID NO. 72)	ACAGTCCGCTCCCTCCTAAT (SEQ ID NO. 73)	26511587	26511825
DG13S69	ATGCTTGGCCCTCAGTTT (SEQ ID NO. 74)	TTGGCAACCCAAGCTAATATG (SEQ ID NO. 75)	26518188	26518483
D13S1250	CTCCACAGTGACAGTGAGG (SEQ ID NO. 76)	GAGAGGTTCCCAATCCC (SEQ ID NO. 77)	26721525	26721686
DG13S574	CAGCTCCTGGCCATATTTCT (SEQ ID NO. 78)	GAGCCATTTCTCTGGGTCTG (SEQ ID NO. 79)	26853541	26853693
DG13S73	GGTCCGTGTCAACCCCTAGA (SEQ ID NO. 80)	CAGGTGTATGGGAGGGAAA (SEQ ID NO. 81)	26878938	26879133
DG13S1532	CGGGAAATGACAGTGAGACC (SEQ ID NO. 82)	TGCCTAGATTCTCCCGTAAG (SEQ ID NO. 83)	26899505	26899652
D13S1242	GTGCCCAGCCAGATTC (SEQ ID NO. 84)	GCCCCAGTCAGGTTT (SEQ ID NO. 85)	26943073	26943316
DG13S576	TTTCTCTCTCCACGGAATGAA (SEQ ID NO. 86)	AACCCATTCTCACAGGGTGA (SEQ ID NO. 87)	27121599	27121797
DG13S1917	AGGAGTGTGGCAGCTTTGAG (SEQ ID NO. 88)	TGGATTTCCCGTGAGTACCAG (SEQ ID NO. 89)	27135092	27135232
D13S217	ATGCTGGGATCACAGGC (SEQ ID NO. 90)	AACCTGGTGGACTTTTGCT (SEQ ID NO. 91)	27169880	27170051
DG13S581	AGCATTCCAATGGTGCTTT (SEQ ID NO. 92)	CATGTTGATATGCCTGAAGGA (SEQ ID NO. 93)	27318359	27318725
DG13S1471	CACTGTCTGCTGCCACTCAT (SEQ ID NO. 94)	AGAGATTATGTGATGTACCCTCTC TAT (SEQ ID NO. 95)	27403303	27403544
DG13S2505	TGATGAAGATCTGGGCGTTA (SEQ ID NO. 96)	TGCCTGTGCTCACTACTCT (SEQ ID NO. 97)	27493479	27493626
D13S120	ATGACCTAGAAATGATACTGGC (SEQ ID NO. 98)	CAGACACCACAACACACATT (SEQ ID NO. 99)	27540983	27541093
D13S1486	TGGTTTAAAAACCTCATGCC (SEQ ID NO. 100)	ATCCCAAACCTGTACTATGTAG G (SEQ ID NO. 101)	27623349	27623496
DG13S1495	CCTTGCTGTTGTGACTGGT (SEQ ID NO. 102)	CACTCAGGTGGGAGGATCAC (SEQ ID NO. 103)	27668199	27668471
DG13S1845	CACCTTGCCAGTAGCCTTGA (SEQ ID NO. 104)	TTGGGAAAGTTAACCCAGAGA (SEQ ID NO. 105)	27788787	27789056
DG13S1030	TTTGGGAAGAGCCATGAGAC (SEQ ID NO. 106)	CTCTGGGCATTGGAGGATTA (SEQ ID NO. 107)	27872811	27873164
DG13S584	GGGAGACAAAGTCAGGTGAGG (SEQ ID NO. 108)	CTGAGTATGGAGTCTTCATCATTA TC (SEQ ID NO. 109)	27924334	27924484
DG13S79	TGCTACTAGATTGACCAACCA (SEQ ID NO. 110)	GACTTGTAAGGATTTAGTGATTT CG (SEQ ID NO. 111)	28213368	28213495
DG13S80	GTGGAAGGCCTCTCTCTGTG (SEQ ID NO. 112)	TGCTTCTTGAGGGAAAGCAT (SEQ ID NO. 113)	28297121	28297353
DG13S1934	CCTTCAGAGGATTTCCCTTTC (SEQ ID NO. 114)	CTGGTTTGACTCCAGCTTCA (SEQ ID NO. 115)	28461787	28462194
DG13S1104	CCTGGCACGGAATAGACACT (SEQ ID NO. 116)	GGCCTCCTTTGCTCTGAAG (SEQ ID NO. 117)	28497694	28498071
DG13S1097	CATCCCTGTGGCTGATTAAGA (SEQ ID NO. 118)	AACAGTTCCAGCCCGTTCTA (SEQ ID NO. 119)	28532382	28532543
DG13S1110	TTTCAAAGGAATATCCAAGTGC (SEQ ID NO. 120)	TGGCGTACCATATAAACAGTTCTC (SEQ ID NO. 121)	28547636	28547900
DG13S87	TTCAATGAAGGTGCCGAAGT (SEQ ID NO. 122)	TGTCTATCCCAAAGCTGCAA (SEQ ID NO. 123)	28597688	28597905
DG13S2400	GCTCAGTCCAAGTTCATGCTC (SEQ ID NO. 124)	TGGGATTGGGTTCTGGATAC (SEQ ID NO. 125)	28671947	28672231

DG13S3114	CCTACTTTCCATCTCCTCCTTG (SEQ ID NO. 126)	TGGAGTAAAGTTGGAGAATTGTTG A (SEQ ID NO. 127)	28678081	28678248
DG13S1111	GCAAGACTCTGTTGAAGAAGAAG A (SEQ ID NO. 128)	TCCCTCTGTTTGAGTTTCTCG (SEQ ID NO. 129)	28760422	28760531
DG13S3122	CCTTGGGCAGTCAGAGAAAC (SEQ ID NO. 130)	CCCGTGAAGTCTGAGAGGTG (SEQ ID NO. 131)	28778662	28778906
DG13S1101	AGGCACAGTCGCTCATGTC (SEQ ID NO. 132)	AAACTTTAGCTAATGGTGGTCAA A (SEQ ID NO. 133)	28812542	28812874
D13S1246	GAGCATGTGTGACTTTCATATTC AG (SEQ ID NO. 134)	AGTGGCTATTCAATTGCTACAGG (SEQ ID NO. 135)	28903534	28903738
DG13S1103	TTGCTGGATGCTGTTTCTA (SEQ ID NO. 136)	AAAGAGAGAGAGAAAGAGAAAG AAAGA (SEQ ID NO. 137)	28910502	28910765
DG13S3147	AAAGTGGATGCAGTTGAGGTTT (SEQ ID NO. 138)	GCTAGCCATTACAGACAACCAA (SEQ ID NO. 139)	29018341	29018591
DG13S3150	CAGGGCTCCATGTATCCATAA (SEQ ID NO. 140)	CAATCTTTGGCTTTGGGTTT (SEQ ID NO. 141)	29042766	29042948
D13S289	CTGGTTGAGCGGCATT (SEQ ID NO. 142)	TGCAGCCTGGATGACA (SEQ ID NO. 143)	29063702	29063949
DG13S166	CCTATGGAAGCATAGGGAAGAA (SEQ ID NO. 144)	CCCCTTCTGAGTCTCCTGAT (SEQ ID NO. 145)	29064359	29064753
DG13S3156	GGGAAATGGAGCTGCTGTTA (SEQ ID NO. 146)	GAGTGGGTGAGTGCAAGGAT (SEQ ID NO. 147)	29111037	29111416
D13S1238	CTCTCAGCAGGCATCCA (SEQ ID NO. 148)	GCCAACGTAATTGACACCA (SEQ ID NO. 149)	29144427	29144579
DG13S2605	TGAAAGGAAGGTCCTGAGTT (SEQ ID NO. 150)	CCCTGCTTTGCACAAGTTATC (SEQ ID NO. 151)	29145896	29146055
DG13S163	CACATGAGGCTGTATGTGGA (SEQ ID NO. 152)	TGTGCGGAATGAGAAGTCG (SEQ ID NO. 153)	29177152	29177313
D13S290	CCTTAGGCCCCATAATCT (SEQ ID NO. 154)	CAAATTCCTCAATTGCAAAAT (SEQ ID NO. 155)	29227323	29227512
D13S1229	GGTCATTCAAGGAGCCATTC (SEQ ID NO. 156)	CCATTATATTTACCAAGAGGCTG C (SEQ ID NO. 157)	29282262	29282396
DG13S2358	AGTCAAGGCTGACAGGGAAG (SEQ ID NO. 158)	GCTCTCAGCCCTCAATGTGT (SEQ ID NO. 159)	29342275	29342399
DG13S2658	ATTTGGGTTCTCTCCCAAT (SEQ ID NO. 160)	ACAACTCTTGCTGCTGGTG (SEQ ID NO. 161)	29348162	29348426
DG13S1460	TGCCTGGTCATCTACCCATT (SEQ ID NO. 162)	TCTACTGCAGCGCTGATCTT (SEQ ID NO. 163)	29389048	29389297
DG13S2434	TCCTCCAGAAGGTTTGCAT (SEQ ID NO. 164)	TGCAAGTTGTTCAAGAGAGACA (SEQ ID NO. 165)	29485254	29485392
DG13S1448	CAGCAGGAAGATGGACAGGT (SEQ ID NO. 166)	CACACTGCATCACACATACCC (SEQ ID NO. 167)	29499404	29499531
D13S1287	TATGCCAGTATGCCTGCT (SEQ ID NO. 168)	GTCACATCAGTCCATTTGC (SEQ ID NO. 169)	29513830	29514063
DG13S2665	GGTTTATGTCTGTGTGTGTGTC (SEQ ID NO. 170)	TGAGGGAATGTCAGAGAAATATGC (SEQ ID NO. 171)	29747845	29747984
DG13S1904	TGATGAAATTGCCTAGTGATGC (SEQ ID NO. 172)	GGATCCAATCGTACGCTACC (SEQ ID NO. 173)	29767797	29767922
DG13S1490	ACCTAAACACCACGACTGG (SEQ ID NO. 174)	CAGGTATCGACATTCTTCCAAA (SEQ ID NO. 175)	29908555	29908958
DG13S2637	GGTGATCTAGGGAATTATTGTC TTC (SEQ ID NO. 176)	TTGGCCAATAAGGTCCAGAT (SEQ ID NO. 177)	29941956	29942120
DG13S96	CCTTTGAGGCTGGATCTGTT (SEQ ID NO. 178)	TTTCCTTATCATTATTCCCTCA (SEQ ID NO. 179)	30166433	30166650
D13S260	AGATAATTGCTCTCGTTCCATGA (SEQ ID NO. 180)	CCCAGATATAAGGACCTGGCTA (SEQ ID NO. 181)	30234833	30234997
DG13S17	TTTAAGCCCTGTGGAATGTATTT (SEQ ID NO. 182)	GACATTGCAGGTCAAGTAGGG (SEQ ID NO. 183)	30288392	30288544
DG13S306	TGCATAAGGCTGGAGACAGA (SEQ ID NO. 184)	CACAGCAGATGGGAGCAAA (SEQ ID NO. 185)	30404049	30404203
DG13S2486	AGCCAGTTGTCTTTCATCCTG (SEQ ID NO. 186)	TGCCTGTGCTTGATATTCTGTG (SEQ ID NO. 187)	30411508	30411755
DG13S18	GTGCATGTGCATACCAGACC (SEQ ID NO. 188)	GGCAAGATGACCTCTGGAAA (SEQ ID NO. 189)	30456875	30457193
DG13S1062	TTTGTGTTCCAGGTGAGAATTG (SEQ ID NO. 190)	GAACCATATCCCAAGGCACT (SEQ ID NO. 191)	30551596	30551715
DG13S1093	TTGTTCCACATTCATTCTACA (SEQ ID NO. 192)	TTAACTCGTGGCAAAGACG (SEQ ID NO. 193)	30625918	30626190

DG13S1059	CACCATGCCTGGCTCTTT (SEQ ID NO. 194)	AACCTCTCCAGTTGTGTGGTTG (SEQ ID NO. 195)	30822917	30823246
D13S171	CCTACCATTGACACTCTCAG (SEQ ID NO. 196)	TAGGGCCATCCATTCT (SEQ ID NO. 197)	31051937	31052167
DG13S2359	TCTGTGTGATTGTGTA CTCTCT G (SEQ ID NO. 198)	TCACACAATTTGAACCAATCCT (SEQ ID NO. 199)	31073673	31073849
DG13S1092	ACCAAGATATGAAGGCCAAA (SEQ ID NO. 200)	CCTCCAGCTAGAACAATGTGAA (SEQ ID NO. 201)	31113759	31113934
DG13S2629	TGATCATGTCAGCAGCAGAAG (SEQ ID NO. 202)	AGTAACAGGTGAGGGCATGG (SEQ ID NO. 203)	31179791	31179953
DG13S1449	TGTCCATAGCTGTAGCCCTGT (SEQ ID NO. 204)	CTCAATGGGCATCTTTAGGC (SEQ ID NO. 205)	31199228	31199498
DG13S312	CAAACAAACAACAAGCAAACC (SEQ ID NO. 206)	TGGACGTTTCTTTCAGTGAGG (SEQ ID NO. 207)	31280202	31280550
DG13S1511	TGATAACTTACCAGCATGTGAGC (SEQ ID NO. 208)	TCACCTCACCTAAGGATCTGC (SEQ ID NO. 209)	31321562	31321854
DG13S2454	GCTAGCAAATCTCTCAACTTCCA (SEQ ID NO. 210)	TCTTCTCCATGCTGCTTCCT (SEQ ID NO. 211)	31352662	31352803
DG13S314	CATGCAATTGCCCAATAGAG (SEQ ID NO. 212)	TTGGCTTGTCTACCTAGTTCA (SEQ ID NO. 213)	31379760	31380086
DG13S1071	GCTGCACGTATTGTGTTGGTG (SEQ ID NO. 214)	AAACAGCAGAAATGGGAACC (SEQ ID NO. 215)	31447431	31447669
DG13S1068	CCGTGGGCTATCAATTTCTG (SEQ ID NO. 216)	AAGATGCAATCTGGTTTCCA (SEQ ID NO. 217)	31553333	31553570
DG13S1077	CCCAAGACTGAGGAGGTCAA (SEQ ID NO. 218)	GCTGACGGAGAGGAAAGAGA (SEQ ID NO. 219)	31569360	31569733
DG13S2343	TCACAAAGCAAGCAATCACA (SEQ ID NO. 220)	TGATGGATGCACCATGTTTA (SEQ ID NO. 221)	31653489	31653608
DG13S316	TGAGAAGCCTGGGCATTAAG (SEQ ID NO. 222)	ACAAGCTCATCCAGGAAAG (SEQ ID NO. 223)	31708002	31708244
DG13S1558	AGAGCTGATCTGGCCGAAG (SEQ ID NO. 224)	GGTGGACACAGAATCCACACT (SEQ ID NO. 225)	31986248	31986627
D13S267	GGCCTGAAAGGTATCCTC (SEQ ID NO. 226)	TCCCACCATAAGCACAAG (SEQ ID NO. 227)	32062233	32062380
DG13S1478	TCAACCTAGGATTGGCATTACA (SEQ ID NO. 228)	TCTAGGATTTGTGCCTTTCCA (SEQ ID NO. 229)	32157761	32158137
DG13S1551	ATTCGTGCAGCTGTTTCTGC (SEQ ID NO. 230)	GCATGACATTGTAAATGGAGGA (SEQ ID NO. 231)	32364898	32365153
DG13S1884	GGTGGGAATGTGTACTGAA (SEQ ID NO. 232)	CCAGGTACAACATTCTCTGAT (SEQ ID NO. 233)	32451203	32451315
D13S1293	TGCAGGTGGGAGTCAA (SEQ ID NO. 234)	AAATAACAAGAAGTGACCTTCT A (SEQ ID NO. 235)	32536337	32536467
DG13S1518	AAAGGATGCATTGGTTAGAG (SEQ ID NO. 236)	ACTGCTCTGTGCTGTGCTT (SEQ ID NO. 237)	32588965	32589321
D13S620	GTCCACCTAATGGCTCATTC (SEQ ID NO. 238)	CAAGAAGCACTCATGTTTGTG (SEQ ID NO. 239)	32627749	32627947
DG13S1866	AGCCTGTGATTGGCTGAGA (SEQ ID NO. 240)	GGCTTACAGCTGCCTCCTTT (SEQ ID NO. 241)	32633306	32633709
DG13S1927	CCCACAGAGCACTTTGTTAGA (SEQ ID NO. 242)	GCCTCCCTTAAGCTGTTATGC (SEQ ID NO. 243)	32691932	32692304
DG13S1503	CACTCTTTACTGCCAATCACTCC (SEQ ID NO. 244)	GCCGTGTGGGTGTATGAAT (SEQ ID NO. 245)	32699827	32700058
DG13S332	TTGTACCAGGAACCAAAGACAA (SEQ ID NO. 246)	CACAGACAGAGGCACATTGA (SEQ ID NO. 247)	32764576	32764751
DG13S333	GCTCTGGTCACTCCTGCTGT (SEQ ID NO. 248)	CATGCCTGGCTGATTGTTT (SEQ ID NO. 249)	32872275	32872720
D13S220	CCAACATCGGGAAGT (SEQ ID NO. 250)	TGCATTCTTTAAGTCCATGTC (SEQ ID NO. 251)	32967602	32967793
DG13S1919	CAGCAACTGACAATCATCCA (SEQ ID NO. 252)	CCTCAATCCTCAGCTCCAAC (SEQ ID NO. 253)	33014255	33014477
DG13S2383	TGATTGGTTCTGTTGTGCTG (SEQ ID NO. 254)	AGCCCAAGGCTCTGTGAG (SEQ ID NO. 255)	33053369	33053553
DG13S1439	TCCTTCACAGCTTCAAACCTCA (SEQ ID NO. 256)	AGTGAGAAGCTTCCATACTGGT (SEQ ID NO. 257)	33070030	33070264
DG13S335	GCCAACCGTTAGACAAATGA (SEQ ID NO. 258)	CTACATGTGCACCACAACACC (SEQ ID NO. 259)	33102278	33102478
DG13S340	AGTTTATTGCCGCCGAGAG (SEQ ID NO. 260)	ACCCACCACATTCACAAGC (SEQ ID NO. 261)	33124866	33125238



DG13S1496	CGATTGCCATGTCTCTTTGA (SEQ ID NO. 262)	GAGATCTGGCCTGGATTTGT (SEQ ID NO. 263)	33215915	33216066
DG13S347	TCATTGTCAGCACAGAATGAACT (SEQ ID NO. 264)	GGAGGGAGGGAAGAAAGAGA (SEQ ID NO. 265)	33280351	33280688
DG13S339	GGAAGAGGAGATTGACTTGTT (SEQ ID NO. 266)	GGAACACCATCATTCCAACC (SEQ ID NO. 267)	33352425	33352656
DG13S1926	TACAAGCTCCACCGTCCTTC (SEQ ID NO. 268)	TGAGTTGCTGCCTCTTCAAA (SEQ ID NO. 269)	33388692	33388919
DG13S1469	TGCTAATGGGCCAAGGAATA (SEQ ID NO. 270)	GCTAAATGTCCTCATGAATAGCC (SEQ ID NO. 271)	33416571	33416940
DG13S351	TGTCCTGCAGACAGATGGTC (SEQ ID NO. 272)	CCTCCGGAGTAGCTGGATTA (SEQ ID NO. 273)	33497762	33498055
DG13S26	GAGACTGGCCCTCATCTTG (SEQ ID NO. 274)	AAGAAGCCAGAGACAAAGAAATA CA (SEQ ID NO. 275)	33584096	33584425
DG13S30	CATCTATCTTTGGATTCACTGGTG (SEQ ID NO. 276)	TGCTCCCAACATCTTACCAG (SEQ ID NO. 277)	33731684	33732071
DG13S1435	TGTCCTCTGGTCATTTCTATGGT (SEQ ID NO. 278)	CATGAATGAGAAGTGATGAATGG (SEQ ID NO. 279)	33762069	33762285
DG13S356	CAGACACTGTAACTGGCTTCG (SEQ ID NO. 280)	GCCACATTGCTATCAGCGTA (SEQ ID NO. 281)	33908746	33908957
DG13S2316	ATGTGCTGTGGTCCAGATT (SEQ ID NO. 282)	CCTACTACTGCAATTACTCCCTAC C (SEQ ID NO. 283)	33913787	33913954
DG13S357	TGTCATAGGCTTGCGGTATTT (SEQ ID NO. 284)	TTGGTAGGGTCCTTTCCTTT (SEQ ID NO. 285)	33935177	33935378
DG13S1032	GCCTGCTCACTGTTGTTTGA (SEQ ID NO. 286)	CGGTTATCAGAGACTGGTGGT (SEQ ID NO. 287)	33967059	33967269
DG13S1557	GGCTTATTTTCATGTACGGCTA (SEQ ID NO. 288)	GGTTAACTCTACTTAGTCCTGAT GC (SEQ ID NO. 289)	33996100	33996249
DG13S1925	GAACCTGTCAGGCACCTCTT (SEQ ID NO. 290)	CCTGAAGCGCTTGTACTGAA (SEQ ID NO. 291)	34079148	34079570
DG13S360	TTGGCTTCTCGCTCTTTCTT (SEQ ID NO. 292)	AGCCATCAGTCACATGCAAA (SEQ ID NO. 293)	34138872	34139221
DG13S1522	AGATCTCCAGGGCAGAGGAC (SEQ ID NO. 294)	CCTTCTCCCTCCTTCTCTC (SEQ ID NO. 295)	34195314	34195659
DG13S2324	CAGTCAAATGTCTCAACCTTCC (SEQ ID NO. 296)	CTAGCAACATGGCCAAGAAA (SEQ ID NO. 297)	34224040	34224206
DG13S1517	CGTCATTGATCCCAATCATCT (SEQ ID NO. 298)	GGCTGATAGCCTCCCTTGTA (SEQ ID NO. 299)	34271358	34271587
DG13S364	ACCTTTCAAGCTTCCGGTTT (SEQ ID NO. 300)	TTCCATCCGTCCATCTATCC (SEQ ID NO. 301)	34323307	34323478
DG13S1036	TTAAAGTCACTTGTCTGTGGTCA (SEQ ID NO. 302)	TTTGTAGGAATCAAGTCAAATAAT GTA (SEQ ID NO. 303)	34525065	34525280
DG13S1037	CTTTCGGAAGCTTGAGCCTA (SEQ ID NO. 304)	CCCAAGACCACTGCCATATT (SEQ ID NO. 305)	34616658	34616926
DG13S1854	TGACAGGTTTGGGTATATTGGA (SEQ ID NO. 306)	TGCTTAATGTAGTGGCAGCA (SEQ ID NO. 307)	34622055	34622151
DG13S1038	TCCTGCCTTTGTGAATTCCT (SEQ ID NO. 308)	GTTGAATGAGGTGGGCATTA (SEQ ID NO. 309)	34702405	34702738
DG13S2366	TTGGGAATAAATCAGGTGTTGA (SEQ ID NO. 310)	GCAGCAGCTCAGCATTTCTC (SEQ ID NO. 311)	34735455	34735583
DG13S1039	CCATTTAATCCTCCAGCCATT (SEQ ID NO. 312)	GCTCCACCTTGTTACCCTGA (SEQ ID NO. 313)	34743651	34743817
DG13S1840	ACAACCTTGGAACTCTGGACT (SEQ ID NO. 314)	GAAGGAAAGGAAAGGAAAGAAA (SEQ ID NO. 315)	34805466	34805682
DG13S369	TGACAAGACTGAAACTTCATCAG (SEQ ID NO. 316)	GATGCTTGCTTTGGGAGGTA (SEQ ID NO. 317)	34815499	34815755
DG13S2481	CAGGTTAGAGCCCATCCAAG (SEQ ID NO. 318)	AGGCTCAGCTTCAATCCACAT (SEQ ID NO. 319)	34867728	34867872
D13S219	AAGCAAATATGCAAAATTGC (SEQ ID NO. 320)	TCCTTCTGTTTCTTGAATTAACA (SEQ ID NO. 321)	34956581	34956707
DG13S2351	GGAACAGGTCACAGGTCAT (SEQ ID NO. 322)	GGAAGACTGGGTGGTCACAG (SEQ ID NO. 323)	35099146	35099320
DG13S384	TTCTTCTGCTTGTGAGCTG (SEQ ID NO. 324)	TACCTCACCTTCCTCATGC (SEQ ID NO. 325)	35499548	35499763
DG13S1507	GAAGACATTGGCAGGTCTGG (SEQ ID NO. 326)	GAGCCCTCATGTTGGGATAA (SEQ ID NO. 327)	35557977	35558206
DG13S1512	TTGTTGATTCTCCATTCTGTG (SEQ ID NO. 328)	TCACCTACCTCATCTCATACTCAA A (SEQ ID NO. 329)	35668964	35669201

DG13S1556	TCITCCGGACAAGTTTCCAA (SEQ ID NO. 330)	TGGGTCAATTCTGGACATTCA (SEQ ID NO. 331)	35791215	35791467
DG13S388	GCAAAATGAGGCTGGTAAGGT (SEQ ID NO. 332)	TGCACTGTGGTAGAGGGAAA (SEQ ID NO. 333)	35817061	35817320
DG13S1442	CAACATACTCCTATGCCTAGAAA GAAA (SEQ ID NO. 334)	CTCACCAGGCAGAAAACAGGT (SEQ ID NO. 335)	35842967	35843335
DG13S1045	CCCAATGGCATGCTTCACT (SEQ ID NO. 336)	GGTTCTCCAGCATTGGTT (SEQ ID NO. 337)	35928180	35928324
DG13S2452	AAGGCCTCTGGGTAGGTAGG (SEQ ID NO. 338)	AAGCAATCCTTATGGGCTCT (SEQ ID NO. 339)	35948528	35948826
DG13S2350	CCAGGTAATCAGAAGCCTCA (SEQ ID NO. 340)	TTCCGTTAAATCCAGCCATC (SEQ ID NO. 341)	36011840	36011961
DG13S2483	CAGGGACTGCAGTGTCTCAA (SEQ ID NO. 342)	ATGCCACATTTGCCTCTCTC (SEQ ID NO. 343)	36027396	36027703
DG13S1100	CCACCTTCCACTTAATACAACT TC (SEQ ID NO. 344)	GAAGCAATCCATTCCAAGAAA (SEQ ID NO. 345)	36056838	36057115
DG13S1501	GTCCTGAGGGTGTCCAGGTA (SEQ ID NO. 346)	GCTGGAGAACTCCTATTCTGCT (SEQ ID NO. 347)	36215761	36215909
DG13S1868	TGGAGCTATTGCGGTTCTCT (SEQ ID NO. 348)	TCAAATCTCTCTTTCCTCCTCT (SEQ ID NO. 349)	36313203	36313417
DG13S395	CAGTTCCAGCTACGGGAGAA (SEQ ID NO. 350)	CCGCATTTAGGCAAGTCTCA (SEQ ID NO. 351)	36317151	36317507
D13S1491	AAGCACACACAGATGCTAGG (SEQ ID NO. 352)	CCTCAGCCTCCATAATCTCA (SEQ ID NO. 353)	36361442	36361571
DG13S400	GTACAGAGCCCACCTTCTGG (SEQ ID NO. 354)	TCACTATGCTGCAAGGCAAG (SEQ ID NO. 355)	36369862	36370134
D13S894	GGTGCTTGCTGTAAATATAATTG (SEQ ID NO. 356)	CACTACAGCAGATTGCACCA (SEQ ID NO. 357)	36536509	36536706
D13S218	GATTTGAAAATGAGCAGTCC (SEQ ID NO. 358)	GTCGGGCACTACGTTTATCT (SEQ ID NO. 359)	36830331	36830519
DG13S1553	TGGGTGAAGATGCTACCTGA (SEQ ID NO. 360)	CCCTTCTTCTTTCCTCTC (SEQ ID NO. 361)	36898814	36899040
DG13S411	TGCCAGGTCTGAGTTGTAAGC (SEQ ID NO. 362)	CAGCATGAGACCCTGTCAA (SEQ ID NO. 363)	36908058	36908265
DG13S1870	GAAAGAAAGAAAGAAAGAA AGAAA (SEQ ID NO. 364)	AATCACCAAACCTGGAAGCA (SEQ ID NO. 365)	36927423	36927632
DG13S1870	GAAAGAAAGAAAGAAAGAA AGAAA (SEQ ID NO. 366)	AATCACCAAACCTGGAAGCA (SEQ ID NO. 367)	36927485	36927632
DG13S39	TCTGAGTTAAACACTTGAGTTGC TG (SEQ ID NO. 368)	CCAGTAAATGGCAGTGTGGTT (SEQ ID NO. 369)	36957292	36957640
DG13S2415	TGTCATGGATATTCTACATAAA CCAA (SEQ ID NO. 370)	TGAAGATGGTTATTGCTTCCTTC (SEQ ID NO. 371)	36984719	36984955
DG13S412	CGCTTTGTTTGGTTT (SEQ ID NO. 372)	ATGCAGTTGTCCACATGCT (SEQ ID NO. 373)	37036929	37037137
DG13S414	TCCTGCACTCCAAAGGAAAC (SEQ ID NO. 374)	AACTCTGGTTTAAATTCAGCTTGT C (SEQ ID NO. 375)	37047489	37047713
DG13S1872	TTCTTGAGGGCATAAAGCTGA (SEQ ID NO. 376)	CACACTCACCAGGCACTCTG (SEQ ID NO. 377)	37119505	37119608
DG13S416	CAGGTTTGATGAAGGAAATATGC (SEQ ID NO. 378)	GGGATCCTCTGCATTTCTCTAA (SEQ ID NO. 379)	37125983	37126184
DG13S2607	TTTGCCAAATCAACCTTCAG (SEQ ID NO. 380)	CCTGCTTCACACCTCTGACC (SEQ ID NO. 381)	37317455	37317831
DG13S1898	ACTCACACACAACCACCACA (SEQ ID NO. 382)	GCTACTGGTGGGTCGTAAGC (SEQ ID NO. 383)	37318932	37319055
D13S1288	TTGAGAGACCATCACGGC (SEQ ID NO. 384)	CTGGAATAATCAGTTGAATCTA GC (SEQ ID NO. 385)	37321295	37321486
DG13S2567	AGGAAAGCCGAGAAAGCATA (SEQ ID NO. 386)	CATGTATCCACATGCCCAGA (SEQ ID NO. 387)	37416093	37416462
DG13S418	CCTTCAGCGCAGCTACATCT (SEQ ID NO. 388)	AGAACTGCGAGGTCCAAGTG (SEQ ID NO. 389)	37473016	37473380
DG13S419	GGGAGAAAGAGAGGTAGGAAGG (SEQ ID NO. 390)	TTCCCAAGTTAGCAGCATCC (SEQ ID NO. 391)	37532947	37533123
DG13S1051	TTCTAGAGGAGTCTATTTCTTAC TGG (SEQ ID NO. 392)	GGAGCTGTCACTTGAGCTTTG (SEQ ID NO. 393)	37694432	37694579
DG13S1841	CCGTGACCTACAGGGAACAT (SEQ ID NO. 394)	GGCATCGGGTGTCTTCTATT (SEQ ID NO. 395)	37715601	37715829
DG13S1052	AGACCTGCCTGTGTTCTGGT (SEQ ID NO. 396)	GGAGTGAAATAAGTGGAAGTGA (SEQ ID NO. 397)	37831275	37831438

DG13S1053	CATTAAATGAGTCATAAAGGTCA TGG (SEQ ID NO. 398)	AACATTGTTGCTTTGCTGGA (SEQ ID NO. 399)	37935190	37935311
DG13S423	GGCCTTAGCTCAGTTTCTGG (SEQ ID NO. 400)	TGCAAAGACATTTGCGGATA (SEQ ID NO. 401)	37941221	37941411
D13S1253	CCTGCATTTGTGTACGTGT (SEQ ID NO. 402)	CAGAGCCGTGGTAGTATATTTT (SEQ ID NO. 403)	37944396	37944533
DG13S2539	GGAACCAAGTCATTGGGTGT (SEQ ID NO. 404)	TTATTGCTCCCTCGTCCAAG (SEQ ID NO. 405)	38050898	38051253
DG13S2509	TGCCTTAAGGTCTATTATTCCTT TC (SEQ ID NO. 406)	ACCAATGCAGGAAGACTCAA (SEQ ID NO. 407)	38067039	38067186
DG13S1863	CTGATGAAAGGACACACATGC (SEQ ID NO. 408)	TGCATTAACTATGCAGCTTGAAA (SEQ ID NO. 409)	38092085	38092353
DG13S2510	GTCGTGCAATCCCGAGAG (SEQ ID NO. 410)	GGATTCTGCTGGCTCTTCT (SEQ ID NO. 411)	38197807	38198059
DG13S1909	CTGGTGTGGTCAGGAAATGA (SEQ ID NO. 412)	GTGTAAACACATGTGAGTGAGA (SEQ ID NO. 413)	38309328	38309442
DG13S428	TTTGACCATGCTTTCTCTTTGA (SEQ ID NO. 414)	GCITGATGACTCCCTGCTGT (SEQ ID NO. 415)	38346716	38347069
DG13S1858	AAGCCATTGAAAGGCAGGTA (SEQ ID NO. 416)	GGGACTTCCGGCTTCTATT (SEQ ID NO. 417)	38371574	38371742
DG13S1911	GGTTTGGGAACCATCTCTCT (SEQ ID NO. 418)	GCAGAGAAGGGATTACTCCAG (SEQ ID NO. 419)	38475656	38475877
DG13S433	ACTTGACATGGAGCAAGCTG (SEQ ID NO. 420)	AGCTCATCATGCTGTAAGGAG (SEQ ID NO. 421)	38516056	38516191
DG13S2421	CACAGGCTCTCACATTCTCG (SEQ ID NO. 422)	TGACACTCATCCCTCTGCTG (SEQ ID NO. 423)	38534972	38535357
DG13S2375	TGAGTTTCATAAGTTTACTACCTG CTG (SEQ ID NO. 424)	GGCAGGGAGAAAGGACAAAT (SEQ ID NO. 425)	38548257	38548440
D13S1248	TCCCTTATGTGGGATTAGTTGA (SEQ ID NO. 426)	CAGACATGGAAGTGAATTTTT (SEQ ID NO. 427)	38558005	38558267
DG13S1856	TGTTCCATCTCTACCCATGT (SEQ ID NO. 428)	TCAATGTTCTTATTGAGTGGGAAA (SEQ ID NO. 429)	38577323	38577506
DG13S435	ATATCCACCCACCCACACAT (SEQ ID NO. 430)	TAGCTCTGAGGGCAGAGACC (SEQ ID NO. 431)	38591043	38591261
DG13S2459	CCGTCCTTCTCCACTGAT (SEQ ID NO. 432)	AGAGCACTGAGGGAGCAAAT (SEQ ID NO. 433)	38596056	38596299
DG13S438	AGCTACAGCACGAGGCAGTT (SEQ ID NO. 434)	TTTGAATTGAGTTGCTGTTCTG (SEQ ID NO. 435)	38676957	38677248
DG13S1865	TGTACACCACCAACCATTCTG (SEQ ID NO. 436)	GGGAAGAAAGGCAAATAGCA (SEQ ID NO. 437)	38684800	38684904
DG13S2354	GGATTGGCAATTAGCAGGTC (SEQ ID NO. 438)	GCCTGGTCAAAGATAACAGACG (SEQ ID NO. 439)	38773862	38774026
DG13S2534	CCTGATTAAGCTGGCCTTTG (SEQ ID NO. 440)	ATCCTTCTGGGACCCCTCATC (SEQ ID NO. 441)	38801698	38801951
DG13S1903	GCTTTGCTTCTTCTTGGTG (SEQ ID NO. 442)	CAACATTACGGCCAGTCTCA (SEQ ID NO. 443)	38802843	38803052
DG13S1896	GGTGCATCTGATAAGCCAAA (SEQ ID NO. 444)	GCTGTCTTGGACACAGTGGA (SEQ ID NO. 445)	38815291	38815405
DG13S443	CACCATCATCATCTGGTTGG (SEQ ID NO. 446)	GAGCTATTGAAAGCGACGA (SEQ ID NO. 447)	38838839	38839093
DG13S445	CCATCCATCTATCCATTATCTCT G (SEQ ID NO. 448)	GGATTTATCCTTGCCCTGCT (SEQ ID NO. 449)	38840399	38840584
DG13S447	CTATCATCCATCCATCCTATTG (SEQ ID NO. 450)	TTAGGGCAGCTACCTGGAAA (SEQ ID NO. 451)	38840751	38840928
D13S1233	AGGACTANAGATGAATGCTC (SEQ ID NO. 452)	GACATGACTCCATGTTTGGT (SEQ ID NO. 453)	38875108	38875292
DG13S2320	CCTCACCTTGCAATTTCTG (SEQ ID NO. 454)	CTGACTTGCCCTGTTGGCATA (SEQ ID NO. 455)	38957405	38957570
DG13S451	TTTGGGATCTGAAGACCTTT (SEQ ID NO. 456)	TTGTGGCATGTCCTTGGTT (SEQ ID NO. 457)	39032835	39033191
DG13S180	TGTAACTGCAAACATTGCTAAA (SEQ ID NO. 458)	TTGTCTTTCATTATGACGTGTCT (SEQ ID NO. 459)	39233968	39234350
DG13S458	AAGCCTGAAAGGATACACAAA A (SEQ ID NO. 460)	CAGGATCCAGACTTCCAG (SEQ ID NO. 461)	39475899	39476187
DG13S2547	GGTGAATCCCACCCTCATAC (SEQ ID NO. 462)	TTGGTATGTTTCTATTGTTGCAT (SEQ ID NO. 463)	39612492	39612849
D13S244	GAACCACTGAGTTTTTATTAC (SEQ ID NO. 464)	AGACACAGCATATAATACATG (SEQ ID NO. 465)	39665226	39665353

DG13S2435	TGAAGCTTTGTGGCTTGTG (SEQ ID NO. 466)	GACTGAGTCCACAGCCATT (SEQ ID NO. 467)	39863067	39863301
D13S263	CCTGGCCTGTTAGTTTTATTGTT A (SEQ ID NO. 468)	CCCAGTCTTGGGTATGTTTTTA (SEQ ID NO. 469)	39878976	39879126
DG13S188	CCACCATGCAAGAACAGATG (SEQ ID NO. 470)	GCTTTGCACTTGGCTGTCTT (SEQ ID NO. 471)	39935769	39936103
DG13S189	TTGCATGAAGTAAAGTATCCCTG T (SEQ ID NO. 472)	CACAAACCACAAGATGATTGG (SEQ ID NO. 473)	39968676	39969030
DG13S190	GGGCATCATGTCTACAACCTCA (SEQ ID NO. 474)	ACCAAGGGCACTTGCTGATA (SEQ ID NO. 475)	40027542	40027801
DG13S2370	AGGATGAAGAGGGAGGAAGG (SEQ ID NO. 476)	CCAGACTGATCTTCCTTAATTAGT TG (SEQ ID NO. 477)	40159684	40159812
DG13S196	CCTCTCTTTCTGCTGCTGT (SEQ ID NO. 478)	AGCCAAAGAACCCAAAGAAAC (SEQ ID NO. 479)	40251445	40251793
DG13S2457	GCCCTACTTTGCCTCAGAAA (SEQ ID NO. 480)	GCAACTCATGCCAGCCTCTA (SEQ ID NO. 481)	40376042	40376447
DG13S2445	AACTGTGTTAATGATGGGCAAA (SEQ ID NO. 482)	AACGAGCGCATGAAACCTAT (SEQ ID NO. 483)	40422793	40423200
DG13S211	CCTGGTCAATTGAACCCAAA (SEQ ID NO. 484)	TGAAGGAAGATAAAGCAGGGTAA (SEQ ID NO. 485)	40434073	40434172
DG13S472	CTCTCTCTGGCCCTCTCTTG (SEQ ID NO. 486)	GGTAACTTGCCATTCTTCTACCA (SEQ ID NO. 487)	40476985	40477395
DG13S207	ACTCCACCTGAAGGGAGAAA (SEQ ID NO. 488)	TGGAAGCCACTAATTGGAGAA (SEQ ID NO. 489)	40545942	40546202
DG13S200	AATGGATGGATACCTCCTTATCA (SEQ ID NO. 490)	CTCATTTGTGGCTTTCTGTGC (SEQ ID NO. 491)	40737337	40737570
DG13S198	GTACCCACACCTACCAAGC (SEQ ID NO. 492)	CGTAGCTCACATTCCTCAACA (SEQ ID NO. 493)	40811813	40812059
DG13S215	GGCGAGTGAAGAGAGGACA (SEQ ID NO. 494)	GGGTGGTAATTCCAGATGA (SEQ ID NO. 495)	40871695	40871992
DG13S221	TCTGCAACAGCCAGAATCAA (SEQ ID NO. 496)	TGTCTGTTGGCAACTTTCTGTC (SEQ ID NO. 497)	41107773	41108117
DG13S219	AGGTGAACCCAGTCCAGCTA (SEQ ID NO. 498)	TCTTAGGCAAAGGAGCCAGT (SEQ ID NO. 499)	41127591	41127734
D13S1270	ACATGAGCACTGGTGACTG (SEQ ID NO. 500)	GGCCTCAAATGTTTAAAGCA (SEQ ID NO. 501)	41161654	41161831
DG13S225	TTCTGGGTGTTGCTATTCC (SEQ ID NO. 502)	TTTCTGTCCAGTCTTGACC (SEQ ID NO. 503)	41212951	41213310
D13S1276	GTTTTCAGGTCTAGGTCACAC (SEQ ID NO. 504)	AGGATAGCTTGAGCCCG (SEQ ID NO. 505)	41213917	41214090

All references cited herein are incorporated by reference in their entirety.

While this invention has been particularly shown and described with references to preferred embodiments thereof, it will be understood by those skilled in the art that various changes in form and details may be made therein without departing from the scope of the invention encompassed by the appended claims.

## CLAIMS

- 5           1.     A method of treatment for myocardial infarction, stroke or PAOD or susceptibility to myocardial infarction, stroke or PAOD in an individual, comprising administering a leukotriene synthesis inhibitor to the individual in need thereof, in a therapeutically effective amount.
- 10           2.     The method of Claim 1, wherein the individual has at least one risk factor selected from the group consisting of: an at-risk haplotype for myocardial infarction, stroke or PAOD; an at-risk haplotype in the FLAP gene; a polymorphism in a FLAP nucleic acid; and an at-risk polymorphism in the 5-LO gene promoter.
- 15           3.     The method of Claim 1, wherein the individual has at least one risk factor selected from the group consisting of: diabetes; hypertension; hypercholesterolemia; elevated triglycerides; elevated lp(a); obesity; ankle/brachial index (ABI) less than 0.9; and past or current smoker.
- 20           4.     The method of Claim 1, wherein the individual has at least one risk factor selected from the group consisting of: a transient ischemic attack; transient monocular blindness; carotid endarterectomy; and asymptomatic carotid stenosis.
- 25           5.     The method of Claim 1, wherein the individual has at least one risk factor selected from the group consisting of: claudication, limb ischemia leading to gangrene, ulceration or amputation; and a revascularization procedure.
- 30           6.     The method of Claim 1, wherein the individual has an elevated inflammatory marker.

7. The method of Claim 6, wherein the inflammatory marker is selected from the group consisting of: C-reactive protein (CRP), serum amyloid A, fibrinogen, a leukotriene, a leukotriene metabolite,  
5 interleukin-6, tissue necrosis factor-alpha, a soluble vascular cell adhesion molecule (sVCAM), a soluble intervascular adhesion molecule (sICAM), E-selectin, matrix metalloprotease type-1, matrix metalloprotease type-2, matrix metalloprotease type-3, matrix metalloprotease type-9, myeloperoxidase (MPO) and N-tyrosine.  
10
8. The method of Claim 1, wherein the individual has increased LDL cholesterol and/or decreased HDL cholesterol.
9. The method of Claim 1, wherein the individual has increased  
15 leukotriene synthesis.
10. The method of Claim 1, wherein the individual has had at least one previous myocardial infarction or ACS event, or has stable angina.
- 20 11. The method of Claim 1, wherein the individual has had at least one previous transient ischemic attack, transient monocular blindness, or stroke.
12. The method of Claim 1, wherein the individual has asymptomatic  
25 carotid stenosis or has had a carotid endarterectomy.
13. The method of Claim 1, wherein the individual has had a revascularization procedure.
- 30 14. The method of Claim 1, wherein the individual has atherosclerosis or who requires treatment (e.g., angioplasty, stents, revascularization procedure) to restore blood flow in arteries.

15. The method of Claim 1, wherein the leukotriene synthesis inhibitor is selected from the group consisting of: 1-((4-chlorophenyl)methyl)-3-  
5 ((1,1-dimethylethyl)thio)-alpha,alpha-dimethyl-5-(2-quinolinylmethoxy)-1H-Indole-2-propanoic acid otherwise known as MK-0591, (R)-(+)-alpha-cyclopentyl-4-(2-quinolinylmethoxy)-Benzeneacetic acid otherwise known as BAY-x-1005, 3-(3-(1,1-dimethylethylthio-5-(quinoline-2-ylmethoxy)-1-(4-chloromethylphenyl)indole-2-yl)-2,2-dimethylpropionaldehyde oxime-  
10 0-2-acetic acid otherwise known as A-81834, optically pure enantiomers, salts, chemical derivatives, and analogues.
16. The method of Claim 1, wherein the leukotriene synthesis inhibitor is selected from the group consisting of: zileuton, atreleuton, 6-((3-  
15 fluoro-5-(tetrahydro-4-methoxy-2H-pyran-4yl)phenoxy)methyl)-1-methyl-2(1H)-quinolinone otherwise known as ZD-2138, 1-((4-chlorophenyl)methyl)-3-((1,1dimethylethyl)thio)-alpha,alpha-dimethyl-5-(2-quinolinylmethoxy)-1H-Indole-2-propanoic acid otherwise known as MK-886, 4-(3-(4-(2-Methyl-imidazol-1-yl)-phenylsulfanyl)-phenyl)-tetrahydro-pyran-4-carboxylic acid amide  
20 otherwise known as CJ-13610, their optically pure enantiomers, salts, chemical derivatives, and analogues.
17. The method of Claim 1, wherein the leukotriene synthesis inhibitor is a  
25 FLAP inhibitor or antagonist.
18. The method of Claim 1, wherein the leukotriene synthesis inhibitor is a 5-LO inhibitor or antagonist.
19. The method of Claim 1, wherein the leukotriene synthesis inhibitor is a  
30 leukotriene inhibitor or antagonist, or an antibody to a leukotriene.

20. The method of Claim 1, wherein the leukotriene synthesis inhibitor is a leukotriene receptor inhibitor or antagonist.
- 5 21. The method of Claim 20, wherein the leukotriene receptor inhibitor or antagonist is an agent that inhibits or antagonizes a receptor selected from the group consisting of: BLT1, BLT2, CysLTR1, and CysLTR2.
22. The method of Claim 1, wherein the leukotriene synthesis inhibitor is an inhibitor of a member of the leukotriene biosynthesis pathway.
- 10 23. The method of Claim 22, wherein the member of the leukotriene biosynthesis pathway is selected from the group consisting of: FLAP, 5-LO, LTC4S, and LTA4H.
- 15 24. A method of treatment for acute coronary syndrome in an individual, comprising administering leukotriene synthesis inhibitor to the individual, in a therapeutically effective amount.
- 20 25. The method of Claim 24, wherein the acute coronary syndrome is selected from the group consisting of: unstable angina, non-ST-elevation myocardial infarction (NSTEMI) and ST-elevation myocardial infarction (STEMI).
- 25 26. The method of Claim 24, wherein the individual has at least one risk factor selected from the group consisting of: an at-risk haplotype for myocardial infarction; an at-risk haplotype in the FLAP gene; a polymorphism in a FLAP nucleic acid; and an at-risk polymorphism in the 5-LO gene promoter.
- 30 27. The method of Claim 24, wherein the individual has at least one risk factor selected from the group consisting of: diabetes; hypertension;



hypercholesterolemia; elevated triglycerides; elevated lp(a); obesity; ankle/brachial index (ABI) less than 0.9; and past or current smoker.

- 5           28.    The method of Claim 24, wherein the individual has an elevated inflammatory marker.
- 10           29.    The method of Claim 28, wherein the inflammatory marker is selected from the group consisting of: C-reactive protein (CRP), serum amyloid A, fibrinogen, a leukotriene, a leukotriene metabolite, interleukin-6, tissue necrosis factor-alpha, a soluble vascular cell adhesion molecule (sVCAM), a soluble intervascular adhesion molecule (sICAM), E-selectin, matrix metalloprotease type-1, matrix metalloprotease type-2, matrix metalloprotease type-3, matrix metalloprotease type-9, myeloperoxidase (MPO) and N-tyrosine.
- 15           30.    The method of Claim 24, wherein the individual has increased LDL cholesterol and/or decreased HDL cholesterol.
- 20           31.    The method of Claim 24, wherein the individual has increased leukotriene synthesis.
32.    The method of Claim 24, wherein the individual has had at least one previous myocardial infarction or ACS event, or has stable angina.
- 25           33.    The method of Claim 24, wherein the individual has atherosclerosis or who requires treatment (*e.g.*, angioplasty, stents, revascularization procedure) to restore blood flow in arteries.
- 30           34.    The method of Claim 24, wherein the leukotriene synthesis inhibitor is selected from the group consisting of: 1-((4-chlorophenyl)methyl)-3-((1,1-dimethylethyl)thio)-alpha,alpha-dimethyl-5-(2-quinolinylmethoxy)-1H-Indole-2-propanoic acid otherwise known as

- 5 MK-0591, (R)-(+)-alpha-cyclopentyl-4-(2-quinolinylmethoxy)-  
Benzeneacetic acid otherwise known as BAY-x-1005, 3-(3-(1,1-  
dimethylethylthio-5-(quinoline-2-ylmethoxy)-1-(4-  
chloromethylphenyl)indole-2-yl)-2,2-dimethylpropionaldehyde oxime-  
0-2-acetic acid otherwise known as A-81834, optically pure  
enantiomers, salts, chemical derivatives, and analogues.
- 10 35. The method of Claim 24, wherein the leukotriene synthesis inhibitor is  
selected from the group consisting of: zileuton, atreleuton, 6-((3-  
fluoro-5-(tetrahydro-4-methoxy-2H-pyran-4yl)phenoxy)methyl)-1-  
methyl-2(1H)-quinololinone otherwise known as ZD-2138, 1-((4-  
chlorophenyl)methyl)-3-((1,1dimethylethyl)thio)-alpha,alpha-  
dimethyl-5-(2-quinolinylmethoxy)-1H-Indole-2-propanoic acid  
otherwise known as MK-886, 4-(3-(4-(2-Methyl-imidazol-1-yl)-  
15 phenylsulfanyl)-phenyl)-tetrahydro-pyran-4-carboxylic acid amide  
otherwise known as CJ-13610, their optically pure enantiomers, salts,  
chemical derivatives, and analogues.
- 20 36. The method of Claim 24, wherein the leukotriene synthesis inhibitor is  
a FLAP inhibitor or antagonist.
37. The method of Claim 24, wherein the leukotriene synthesis inhibitor is  
a 5-LO inhibitor or antagonist.
- 25 38. The method of Claim 24, wherein the leukotriene synthesis inhibitor is  
a leukotriene inhibitor or antagonist, or an antibody to a leukotriene.
39. The method of Claim 24, wherein the leukotriene synthesis inhibitor is  
a leukotriene receptor inhibitor or antagonist.

40. The method of Claim 39, wherein the leukotriene receptor inhibitor or antagonist is an agent that inhibits or antagonizes a receptor selected from the group consisting of: BLT1, BLT2, CysLTR1, and CysLTR2.
- 5 41. The method of Claim 24, wherein the leukotriene synthesis inhibitor is an inhibitor of a member of the leukotriene biosynthesis pathway.
42. The method of Claim 41, wherein the member of the leukotriene biosynthesis pathway is selected from the group consisting of: FLAP,  
10 5-LO, LTC4S, and LTA4H.
43. A method of treatment for transient ischemic attack, transient monocular blindness or stroke in an individual, comprising administering leukotriene synthesis inhibitor to the individual, in a  
15 therapeutically effective amount.
44. The method of Claim 43, wherein the individual has at least one risk factor selected from the group consisting of: an at-risk haplotype for stroke; an at-risk haplotype in the FLAP gene; a polymorphism in a  
20 FLAP nucleic acid; and an at-risk polymorphism in the 5-LO gene promoter.
45. The method of Claim 43, wherein the individual has at least one risk factor selected from the group consisting of: diabetes; hypertension;  
25 hypercholesterolemia; elevated triglycerides; elevated lp(a); obesity; ankle/brachial index (ABI) less than 0.9; and past or current smoker.
46. The method of Claim 43, wherein the individual has an elevated inflammatory marker.
- 30 47. The method of Claim 46, wherein the inflammatory marker is selected from the group consisting of: C-reactive protein (CRP), serum

- amyloid A, fibrinogen, a leukotriene, a leukotriene metabolite, interleukin-6, tissue necrosis factor-alpha, a soluble vascular cell adhesion molecule (sVCAM), a soluble intervascular adhesion molecule (sICAM), E-selectin, matrix metalloprotease type-1, matrix metalloprotease type-2, matrix metalloprotease type-3, matrix metalloprotease type-9, myeloperoxidase (MPO) and N-tyrosine.
- 5
48. The method of Claim 43, wherein the individual has increased LDL cholesterol and/or decreased HDL cholesterol.
- 10
49. The method of Claim 43, wherein the individual has increased leukotriene synthesis.
50. The method of Claim 43, wherein the individual has had at least one previous transient ischemic attack, transient monocular blindness or stroke.
- 15
51. The method of Claim 43, wherein the individual has asymptomatic carotid stenosis or has had a carotid endarterectomy.
- 20
52. The method of Claim 43, wherein the leukotriene synthesis inhibitor is selected from the group consisting of: 1-((4-chlorophenyl)methyl)-3-((1,1-dimethylethyl)thio)-alpha,alpha-dimethyl-5-(2-quinolinylmethoxy)-1H-Indole-2-propanoic acid otherwise known as MK-0591, (R)-(+)-alpha-cyclopentyl-4-(2-quinolinylmethoxy)-Benzeneacetic acid otherwise known as BAY-x-1005, 3-(3-(1,1-dimethylethylthio-5-(quinoline-2-ylmethoxy)-1-(4-chloromethylphenyl)indole-2-yl)-2,2-dimethylpropionaldehyde oxime-0-2-acetic acid otherwise known as A-81834, optically pure enantiomers, salts, chemical derivatives, and analogues.
- 25
- 30

53. The method of Claim 43, wherein the leukotriene synthesis inhibitor is selected from the group consisting of: zileuton, atreleuton, 6-((3-fluoro-5-(tetrahydro-4-methoxy-2H-pyran-4yl)phenoxy)methyl)-1-methyl-2(1H)-quinolinone otherwise known as ZD-2138, 1-((4-chlorophenyl)methyl)-3-((1,1dimethylethyl)thio)-alpha,alpha-dimethyl-5-(2-quinolinylmethoxy)-1H-Indole-2-propanoic acid otherwise known as MK-886, 4-(3-(4-(2-Methyl-imidazol-1-yl)-phenylsulfanyl)-phenyl)-tetrahydro-pyran-4-carboxylic acid amide otherwise known as CJ-13610, their optically pure enantiomers, salts, chemical derivatives, and analogues.
54. The method of Claim 43, wherein the leukotriene synthesis inhibitor is a FLAP inhibitor or antagonist.
55. The method of Claim 43, wherein the leukotriene synthesis inhibitor is a 5-LO inhibitor or antagonist.
56. The method of Claim 43, wherein the leukotriene synthesis inhibitor is a leukotriene inhibitor or antagonist, or an antibody to a leukotriene.
57. The method of Claim 43, wherein the leukotriene synthesis inhibitor is a leukotriene receptor inhibitor or antagonist.
58. The method of Claim 58, wherein the leukotriene receptor inhibitor or antagonist is an agent that inhibits or antagonizes a receptor selected from the group consisting of: BLT1, BLT2, CysLTR1, and CysLTR2.
59. The method of Claim 43, wherein the leukotriene synthesis inhibitor is an inhibitor of a member of the leukotriene biosynthesis pathway.

60. The method of Claim 59, wherein the member of the leukotriene biosynthesis pathway is selected from the group consisting of: FLAP, 5-LO, LTC4S, and LTA4H.
- 5 61. A method of treatment of PAOD or claudication, comprising administering leukotriene synthesis inhibitor to the individual, in a therapeutically effective amount.
- 10 62. The method of Claim 61, wherein the individual has at least one risk factor selected from the group consisting of: an at-risk haplotype for PAOD; an at-risk haplotype in the FLAP gene; a polymorphism in a FLAP nucleic acid; and an at-risk polymorphism in the 5-LO gene promoter.
- 15 63. The method of Claim 61, wherein the individual has at least one risk factor selected from the group consisting of: diabetes; hypertension; hypercholesterolemia; elevated triglycerides; elevated lp(a); obesity; ankle/brachial index (ABI) less than 0.9; and past or current smoker.
- 20 64. The method of Claim 61, wherein the individual has an elevated inflammatory marker.
- 25 65. The method of Claim 64, wherein the inflammatory marker is selected from the group consisting of: C-reactive protein (CRP), serum amyloid A, fibrinogen, a leukotriene, a leukotriene metabolite, interleukin-6, tissue necrosis factor-alpha, a soluble vascular cell adhesion molecule (sVCAM), a soluble intervascular adhesion molecule (sICAM), E-selectin, matrix metalloprotease type-1, matrix metalloprotease type-2, matrix metalloprotease type-3, matrix metalloprotease type-9, myeloperoxidase (MPO) and N-tyrosine.
- 30

66. The method of Claim 61, wherein the individual has increased LDL cholesterol and/or decreased HDL cholesterol.
67. The method of Claim 61, wherein the individual has increased leukotriene synthesis.
68. The method of Claim 61, wherein the individual has been diagnosed previously with a condition selected from the group consisting of: PAOD, claudication, and limb ischemia leading to gangrene, ulceration or amputation.
69. The method of Claim 61, wherein the individual has had a vascular or peripheral artery revascularization graft.
70. The method of Claim 61, wherein the leukotriene synthesis inhibitor is selected from the group consisting of: 1-((4-chlorophenyl)methyl)-3-((1,1-dimethylethyl)thio)-alpha,alpha-dimethyl-5-(2-quinolinylmethoxy)-1H-Indole-2-propanoic acid otherwise known as MK-0591, (R)-(+)-alpha-cyclopentyl-4-(2-quinolinylmethoxy)-Benzeneacetic acid otherwise known as BAY-x-1005, 3-(3-(1,1-dimethylethylthio-5-(quinoline-2-ylmethoxy)-1-(4-chloromethylphenyl)indole-2-yl)-2,2-dimethylpropionaldehyde oxime-0-2-acetic acid otherwise known as A-81834, optically pure enantiomers, salts, chemical derivatives, and analogues.
71. The method of Claim 61, wherein the leukotriene synthesis inhibitor is selected from the group consisting of: zileuton, atreleuton, 6-((3-fluoro-5-(tetrahydro-4-methoxy-2H-pyran-4yl)phenoxy)methyl)-1-methyl-2(1H)-quinolinone otherwise known as ZD-2138, 1-((4-chlorophenyl)methyl)-3-((1,1-dimethylethyl)thio)-alpha,alpha-dimethyl-5-(2-quinolinylmethoxy)-1H-Indole-2-propanoic acid otherwise known as MK-886, 4-(3-(4-(2-Methyl-imidazol-1-yl)-

phenylsulfanyl)-phenyl)-tetrahydro-pyran-4-carboxylic acid amide otherwise known as CJ-13610, their optically pure enantiomers, salts, chemical derivatives, and analogues.

- 5           72.    The method of Claim 61, wherein the leukotriene synthesis inhibitor is a FLAP inhibitor or antagonist.
73.    The method of Claim 61, wherein the leukotriene synthesis inhibitor is a 5-LO inhibitor or antagonist.
- 10           74.    The method of Claim 61, wherein the leukotriene synthesis inhibitor is a leukotriene inhibitor or antagonist, or an antibody to a leukotriene.
75.    The method of Claim 61, wherein the leukotriene synthesis inhibitor is a leukotriene receptor inhibitor or antagonist.
- 15           76.    The method of Claim 75, wherein the leukotriene receptor inhibitor or antagonist is an agent that inhibits or antagonizes a receptor selected from the group consisting of: BLT1, BLT2, CysLTR1, and CysLTR2.
- 20           77.    The method of Claim 61, wherein the leukotriene synthesis inhibitor is an inhibitor of a member of the leukotriene biosynthesis pathway.
78.    The method of Claim 77, wherein the member of the leukotriene biosynthesis pathway is selected from the group consisting of: FLAP, 5-LO, LTC4S, and LTA4H.
- 25           79.    A method of decreasing risk of a subsequent myocardial infarction or stroke in an individual who has had at least one myocardial infarction or stroke, comprising administering a leukotriene synthesis inhibitor to the individual, in a therapeutically effective amount.
- 30



- 5           80.     The method of Claim 79, wherein the individual has at least one risk factor selected from the group consisting of: an at-risk haplotype for myocardial infarction or stroke; an at-risk haplotype in the FLAP gene; a polymorphism in a FLAP nucleic acid; and an at-risk polymorphism in the 5-LO gene promoter.
- 10           81.     The method of Claim 79, wherein the individual has at least one risk factor selected from the group consisting of: diabetes; hypertension; hypercholesterolemia; elevated triglycerides; elevated lp(a); obesity; ankle/brachial index (ABI) less than 0.9; and past or current smoker.
- 15           82.     The method of Claim 79, wherein the individual has at least one risk factor selected from the group consisting of: a transient ischemic attack; transient monocular blindness; carotid endarterectomy; and asymptomatic carotid stenosis.
- 20           83.     The method of Claim 79, wherein the individual has an elevated inflammatory marker.
- 25           84.     The method of Claim 83, wherein the inflammatory marker is selected from the group consisting of: C-reactive protein (CRP), serum amyloid A, fibrinogen, a leukotriene, a leukotriene metabolite, interleukin-6, tissue necrosis factor-alpha, a soluble vascular cell adhesion molecule (sVCAM), a soluble intervascular adhesion molecule (sICAM), E-selectin, matrix metalloprotease type-1, matrix metalloprotease type-2, matrix metalloprotease type-3, matrix metalloprotease type-9, myeloperoxidase (MPO) and N-tyrosine.
- 30           85.     The method of Claim 79, wherein the individual has increased LDL cholesterol and/or decreased HDL cholesterol.

86. The method of Claim 79, wherein the individual has increased leukotriene synthesis.
87. The method of Claim 79, wherein the individual has had at least one previous myocardial infarction or ACS event, or has stable angina.
88. The method of Claim 79, wherein the individual has had at least one previous transient ischemic attack, transient monocular blindness or stroke.
89. The method of Claim 79, wherein the individual has asymptomatic carotid stenosis or has had a carotid endarterectomy.
90. The method of Claim 79, wherein the individual has atherosclerosis or who requires treatment (*e.g.*, angioplasty, stents, revascularization procedure) to restore blood flow in arteries.
91. The method of Claim 79, wherein the leukotriene synthesis inhibitor is selected from the group consisting of: 1-((4-chlorophenyl)methyl)-3-((1,1-dimethylethylthio)-alpha,alpha-dimethyl-5-(2-quinolinylmethoxy)-1H-Indole-2-propanoic acid otherwise known as MK-0591, (R)-(+)-alpha-cyclopentyl-4-(2-quinolinylmethoxy)-Benzeneacetic acid otherwise known as BAY-x-1005, 3-(3-(1,1-dimethylethylthio-5-(quinoline-2-ylmethoxy)-1-(4-chloromethylphenyl)indole-2-yl)-2,2-dimethylpropionaldehyde oxime-0-2-acetic acid otherwise known as A-81834, optically pure enantiomers, salts, chemical derivatives, and analogues.
92. The method of Claim 79, wherein the leukotriene synthesis inhibitor is selected from the group consisting of: zileuton, atreleuton, 6-((3-fluoro-5-(tetrahydro-4-methoxy-2H-pyran-4yl)phenoxy)methyl)-1-methyl-2(1H)-quinolinone otherwise known as ZD-2138, 1-((4-

chlorophenyl)methyl)-3-((1,1dimethylethyl)thio)-alpha,alpha-dimethyl-5-( 2-quinolinylmethoxy)-1H-Indole-2-propanoic acid otherwise known as MK-886, 4-(3-(4-(2-Methyl-imidazol-1-yl)-phenylsulfanyl)-phenyl)-tetrahydro-pyran-4-carboxylic acid amide otherwise known as CJ-13610, their optically pure enantiomers, salts, chemical derivatives, and analogues.

5

93. The method of Claim 79, wherein the leukotriene synthesis inhibitor is a FLAP inhibitor or antagonist.

10

94. The method of Claim 79, wherein the leukotriene synthesis inhibitor is a 5-LO inhibitor or antagonist.

95. The method of Claim 79, wherein the leukotriene synthesis inhibitor is a leukotriene inhibitor or antagonist, or an antibody to a leukotriene.

15

96. The method of Claim 79, wherein the leukotriene synthesis inhibitor is a leukotriene receptor inhibitor or antagonist.

20

97. The method of Claim 96, wherein the leukotriene receptor inhibitor or antagonist is an agent that inhibits or antagonizes a receptor selected from the group consisting of: BLT1, BLT2, CysLTR1, and CysLTR2.

98. The method of Claim 79, wherein the leukotriene synthesis inhibitor is an inhibitor of a member of the leukotriene biosynthesis pathway.

25

99. The method of Claim 98, wherein the member of the leukotriene biosynthesis pathway is selected from the group consisting of: FLAP, 5-LO, LTC4S, and LTA4H.

30

100. A method of treatment for atherosclerosis or PAOD in an individual, comprising administering a leukotriene synthesis inhibitor to the individual, in a therapeutically effective amount.
- 5 101. The method of Claim 100, wherein the individual is concurrently treated to restore blood flow in coronary, carotid or peripheral arteries.
102. The method of Claim 100, wherein the individual has at least one risk factor selected from the group consisting of: an at-risk haplotype for PAOD; an at-risk haplotype in the FLAP gene; a polymorphism in a  
10 FLAP nucleic acid; and an at-risk polymorphism in the 5-LO gene promoter.
103. The method of Claim 100, wherein the individual has at least one risk factor selected from the group consisting of: diabetes; hypertension; hypercholesterolemia; elevated triglycerides; elevated lp(a); obesity; ankle/brachial index (ABI) less than 0.9; and past or current smoker.  
15
104. The method of Claim 100, wherein the individual has at least one risk factor selected from the group consisting of: claudication, limb ischemia leading to gangrene, ulceration or amputation; and a vascular or peripheral artery revascularization graft.  
20
105. The method of Claim 100, wherein the individual has an elevated inflammatory marker.  
25
106. The method of Claim 105, wherein the inflammatory marker is selected from the group consisting of: C-reactive protein (CRP), serum amyloid A, fibrinogen, a leukotriene, a leukotriene metabolite, interleukin-6, tissue necrosis factor-alpha, a soluble vascular cell  
30 adhesion molecule (sVCAM), a soluble intervascular adhesion molecule (sICAM), E-selectin, matrix metalloprotease type-1, matrix

metalloprotease type-2, matrix metalloprotease type-3, matrix metalloprotease type-9, myeloperoxidase (MPO) and N-tyrosine.

107. The method of Claim 100, wherein the individual has increased LDL cholesterol and/or decreased HDL cholesterol.
108. The method of Claim 100, wherein the individual has increased leukotriene synthesis.
109. The method of Claim 100, wherein the individual has been diagnosed previously with a condition selected from the group consisting of: claudication, and limb ischemia leading to gangrene, ulceration or amputation.
110. The method of Claim 100, wherein the individual has had a vascular or peripheral artery revascularization graft.
111. The method of Claim 100, wherein the individual has atherosclerosis or who requires treatment (*e.g.*, angioplasty, stents, revascularization procedure) to restore blood flow in arteries.
112. The method of Claim 100, wherein the leukotriene synthesis inhibitor is selected from the group consisting of: 1-((4-chlorophenyl)methyl)-3-((1,1-dimethylethyl)thio)-alpha,alpha-dimethyl-5-(2-quinolinylmethoxy)-1H-Indole-2-propanoic acid otherwise known as MK-0591, (R)-(+)-alpha-cyclopentyl-4-(2-quinolinylmethoxy)-Benzeneacetic acid otherwise known as BAY-x-1005, 3-(3-(1,1-dimethylethylthio-5-(quinoline-2-ylmethoxy)-1-(4-chloromethylphenyl)indole-2-yl)-2,2-dimethylpropionaldehyde oxime-0-2-acetic acid otherwise known as A-81834, optically pure enantiomers, salts, chemical derivatives, and analogues.

113. The method of Claim 100, wherein the leukotriene synthesis inhibitor is selected from the group consisting of: zileuton, atreleuton, 6-((3-fluoro-5-(tetrahydro-4-methoxy-2H-pyran-4yl)phenoxy)methyl)-1-methyl-2(1H)-quinolinone otherwise known as ZD-2138, 1-((4-chlorophenyl)methyl)-3-((1,1dimethylethyl)thio)-alpha,alpha-dimethyl-5-(2-quinolinylmethoxy)-1H-Indole-2-propanoic acid otherwise known as MK-886, 4-(3-(4-(2-Methyl-imidazol-1-yl)-phenylsulfanyl)-phenyl)-tetrahydro-pyran-4-carboxylic acid amide otherwise known as CJ-13610, their optically pure enantiomers, salts, chemical derivatives, and analogues.
114. The method of Claim 100, wherein the leukotriene synthesis inhibitor is a FLAP inhibitor or antagonist.
115. The method of Claim 100, wherein the leukotriene synthesis inhibitor is a 5-LO inhibitor or antagonist.
116. The method of Claim 100, wherein the leukotriene synthesis inhibitor is a leukotriene inhibitor or antagonist, or an antibody to a leukotriene.
117. The method of Claim 100, wherein the leukotriene synthesis inhibitor is a leukotriene receptor inhibitor or antagonist.
118. The method of Claim 117, wherein the leukotriene receptor inhibitor or antagonist is an agent that inhibits or antagonizes a receptor selected from the group consisting of: BLT1, BLT2, CysLTR1, and CysLTR2.
119. The method of Claim 100, wherein the leukotriene synthesis inhibitor is an inhibitor of a member of the leukotriene biosynthesis pathway.

120. The method of Claim 119, wherein the member of the leukotriene biosynthesis pathway is selected from the group consisting of: FLAP, 5-LO, LTC4S, and LTA4H.
- 5 121. A method of reducing leukotriene synthesis in an individual, comprising administering a leukotriene synthesis inhibitor to the individual in a therapeutically effective amount.
- 10 122. The method of Claim 121, wherein the individual is concurrently treated to restore blood flow in coronary, carotid or peripheral arteries.
- 15 123. The method of Claim 121, wherein the individual has at least one risk factor selected from the group consisting of: an at-risk haplotype for myocardial infarction, stroke or PAOD; an at-risk haplotype in the FLAP gene; a polymorphism in a FLAP nucleic acid; and an at-risk polymorphism in the 5-LO gene promoter.
- 20 124. The method of Claim 121, wherein the individual has at least one risk factor selected from the group consisting of: diabetes; hypertension; hypercholesterolemia; elevated triglycerides; elevated lp(a); obesity; ankle/brachial index (ABI) less than 0.9; and past or current smoker.
- 25 125. The method of Claim 121, wherein the individual has at least one risk factor selected from the group consisting of: a transient ischemic attack; transient monocular blindness; carotid endarterectomy; and asymptomatic carotid stenosis.
- 30 126. The method of Claim 121, wherein the individual has at least one risk factor selected from the group consisting of: claudication, limb ischemia leading to gangrene, ulceration or amputation; and a vascular or peripheral artery revascularization graft.

127. The method of Claim 121, wherein the individual has an elevated inflammatory marker.
- 5 128. The method of Claim 127, wherein the inflammatory marker is selected from the group consisting of: C-reactive protein (CRP), serum amyloid A, fibrinogen, a leukotriene, a leukotriene metabolite, interleukin-6, tissue necrosis factor-alpha, a soluble vascular cell adhesion molecule (sVCAM), a soluble intervascular adhesion molecule (sICAM), E-selectin, matrix metalloprotease type-1, matrix metalloprotease type-2, matrix metalloprotease type-3, matrix metalloprotease type-9, myeloperoxidase (MPO) and N-tyrosine.
- 10 129. The method of Claim 121, wherein the individual has increased LDL cholesterol and/or decreased HDL cholesterol.
- 15 130. The method of Claim 121, wherein the individual has increased leukotriene synthesis.
- 20 131. The method of Claim 121, wherein the individual has had at least one previous myocardial infarction or ACS event, or has stable angina.
- 25 132. The method of Claim 121, wherein the individual has had at least one previous transient ischemic attack, transient monocular blindness or stroke.
- 30 133. The method of Claim 121, wherein the individual has asymptomatic carotid stenosis or has had a carotid endarterectomy.
134. The method of Claim 121, wherein the individual has had a vascular or peripheral artery revascularization graft.



135. The method of Claim 121, wherein the individual has atherosclerosis or who requires treatment (e.g., angioplasty, stents, revascularization procedure) to restore blood flow in arteries.
- 5 136. The method of Claim 121, wherein the leukotriene synthesis inhibitor is selected from the group consisting of: 1-((4-chlorophenyl)methyl)-3-((1,1-dimethylethyl)thio)-alpha,alpha-dimethyl-5-(2-quinolinylmethoxy)-1H-Indole-2-propanoic acid otherwise known as MK-0591, (R)-(+)-alpha-cyclopentyl-4-(2-quinolinylmethoxy)-  
10 Benzeneacetic acid otherwise known as BAY-x-1005, 3-(3-(1,1-dimethylethylthio-5-(quinoline-2-ylmethoxy)-1-(4-chloromethylphenyl)indole-2-yl)-2,2-dimethylpropionaldehyde oxime-0-2-acetic acid otherwise known as A-81834, optically pure enantiomers, salts, chemical derivatives, and analogues.
- 15 137. The method of Claim 121, wherein the leukotriene synthesis inhibitor is selected from the group consisting of: zileuton, atreleuton, 6-((3-fluoro-5-(tetrahydro-4-methoxy-2H-pyran-4yl)phenoxy)methyl)-1-methyl-2(1H)-quinolinone otherwise known as ZD-2138, 1-((4-  
20 chlorophenyl)methyl)-3-((1,1dimethylethyl)thio)-alpha,alpha-dimethyl-5-(2-quinolinylmethoxy)-1H-Indole-2-propanoic acid otherwise known as MK-886, 4-(3-(4-(2-Methyl-imidazol-1-yl)-phenylsulfanyl)-phenyl)-tetrahydro-pyran-4-carboxylic acid amide otherwise known as CJ-13610, their optically pure enantiomers, salts,  
25 chemical derivatives, and analogues.
138. The method of Claim 121, wherein the leukotriene synthesis inhibitor is a FLAP inhibitor or antagonist.
- 30 139. The method of Claim 121, wherein the leukotriene synthesis inhibitor is a 5-LO inhibitor or antagonist.

140. The method of Claim 121, wherein the leukotriene synthesis inhibitor is a leukotriene inhibitor or antagonist, or an antibody to a leukotriene.
- 5 141. The method of Claim 121, wherein the leukotriene synthesis inhibitor is a leukotriene receptor inhibitor or antagonist.
- 10 142. The method of Claim 141, wherein the leukotriene receptor inhibitor or antagonist is an agent that inhibits or antagonizes a receptor selected from the group consisting of: BLT1, BLT2, CysLTR1, and CysLTR2.
143. The method of Claim 121, wherein the leukotriene synthesis inhibitor is an inhibitor of a member of the leukotriene biosynthesis pathway.
- 15 144. The method of Claim 143, wherein the member of the leukotriene biosynthesis pathway is selected from the group consisting of: FLAP, 5-LO, LTC4S, and LTA4H.
- 20 145. The method of any one of Claims 1-144, wherein the leukotriene synthesis inhibitor is an agent set forth in the Agent Table.
- 25 146. The method of any one of Claims 1-144, wherein the leukotriene synthesis inhibitor is an agent selected from the group consisting of: a complement of a nucleic acid encoding a member of the leukotriene pathway; a binding agent of a member of the leukotriene pathway; an agent that alters expression of a nucleic acid encoding a member of the leukotriene pathway; an agent that alters posttranslational processing of a member of the leukotriene pathway; an agent that alters activity of a polypeptide member of the leukotriene pathway; an agent that alters activity of a leukotriene; an antibody to a leukotriene; and an agent that
- 30 alters interaction among two or more members of the leukotriene pathway.

147. The method of any one of Claims 1-144, wherein the leukotriene synthesis inhibitor is an agent selected from the group consisting of: a FLAP nucleic acid binding agent; a 5-lipoxygenase binding agent; a leukotriene synthetase binding agent; a FLAP nucleic acid binding agent; a 5-lipoxygenase nucleic acid binding agent; a leukotriene synthetase nucleic acid binding agent; a peptidomimetic; a fusion protein; a prodrug; an antibody; an agent that alters FLAP nucleic acid expression; an agent that alters activity of a polypeptide encoded by a FLAP nucleic acid, a 5-lipoxygenase nucleic acid, or a leukotriene synthetase nucleic acid; an agent that alters posttranscriptional processing of a polypeptide encoded by a FLAP nucleic acid, a 5-lipoxygenase nucleic acid or a leukotriene synthetase nucleic acid; an agent that alters interaction of a FLAP nucleic acid with a FLAP nucleic acid binding agent; an agent that alters interaction of a 5-lipoxygenase nucleic acid with a 5-lipoxygenase nucleic acid binding agent; an agent that alters interaction of a leukotriene synthetase nucleic acid with a leukotriene synthetase nucleic acid binding agent; an agent that alters transcription of splicing variants encoded by a FLAP nucleic acid, a 5-lipoxygenase nucleic acid, or a leukotriene synthetase nucleic acid; and ribozymes.
148. A method of assessing an individual for an increased risk of MI, comprising assessing the level of a leukotriene metabolite in the individual, wherein an increased level of leukotriene metabolite is indicative of an increased risk of MI.
149. The method of Claim 148, wherein the leukotriene metabolite is selected from the group consisting of: LTE<sub>4</sub>, LTD<sub>4</sub>, and LTB<sub>4</sub>.
150. The method of Claim 148, wherein the level of the leukotriene metabolite is measured in blood, serum, plasma or urine.

- 5
151. A method of assessing an individual for an increased risk of ACS, comprising assessing the levels of leukotriene metabolites in the individual, wherein an increased level of leukotriene metabolites is indicative of an increased risk of ACS.
152. The method of Claim 151, wherein the leukotriene metabolite is selected from the group consisting of: LTE4, LTD4 and LTB4.
- 10 153. The method of Claim 151, wherein the level of the leukotriene metabolite is measured in blood, serum, plasma or urine.
- 15 154. A method of assessing an individual for an increased risk of atherosclerosis, comprising assessing the levels of leukotriene metabolites in the individual, wherein an increased level of leukotriene metabolites is indicative of an increased risk of atherosclerosis.
155. The method of Claim 154, wherein the leukotriene metabolite is selected from the group consisting of: LTE4, LTD4 and LTB4.
- 20 156. The method of Claim 154, wherein the level of the leukotriene metabolite is measured in blood, serum, plasma or urine.
- 25 157. A method of assessing an individual for an increased risk of stroke, transient ischemic attack, transient monocular blindness or asymptomatic carotid stenosis, comprising assessing the level of a leukotriene metabolite in the individual, wherein an increased level of leukotriene metabolites is indicative of an increased risk of stroke, transient ischemic attack, transient monocular blindness or asymptomatic carotid stenosis.
- 30 158. The method of Claim 157, wherein the leukotriene metabolite is selected from the group consisting of: LTE4, LTD4 and LTB4.

159. The method of Claim 157, wherein the level of the leukotriene metabolite is measured in blood, serum, plasma or urine.
- 5 160. A method of assessing an individual for an increased risk of PAOD, claudication, or limb ischemia, comprising assessing the level of a leukotriene metabolite in the individual, wherein an increased level of leukotriene metabolites is indicative of an increased risk of PAOD, claudication, or limb ischemia.
- 10 161. The method of Claim 160, wherein the leukotriene metabolite is selected from the group consisting of: LTE4, LTD4 and LTB4.
- 15 162. The method of Claim 160, wherein the level of the leukotriene metabolite is measured in blood, serum, plasma or urine.
163. A method of assessing an individual for an increased risk of MI, comprising:
- 20 i. stimulating production of a leukotriene or a leukotriene metabolite in a test sample from the individual, using a calcium ionophore;
- ii. comparing the level of production of the leukotriene or leukotriene metabolite with a control level,
- 25 wherein a level of production of the leukotriene or leukotriene metabolite that is significantly greater than the control level, is indicative of an increased risk of MI.
164. The method of Claim 163, wherein a level of a leukotriene metabolite is compared, and the leukotriene metabolite is selected from the group consisting of: LTE4, LTD4, and LTB4.
- 30

165. The method of Claim 163, wherein the test sample comprises neutrophils.
166. A method of assessing an individual for an increased risk of ACS,  
5 comprising:  
    i. stimulating production of a leukotriene or a leukotriene metabolite in a test sample from the individual, using a calcium ionophore;  
    ii. comparing the level of production of the leukotriene or  
10 leukotriene metabolite with a control level,  
wherein a level of production of the leukotriene or leukotriene metabolite that is significantly greater than the control level, is indicative of an increased risk of ACS.
167. The method of Claim 166, wherein a level of a leukotriene metabolite  
15 is compared, and the leukotriene metabolite is selected from the group consisting of: LTE<sub>4</sub>, LTD<sub>4</sub> and LTB<sub>4</sub>.
168. The method of Claim 166, wherein test sample comprises neutrophils.  
20
169. A method of assessing an individual for an increased risk of atherosclerosis, comprising:  
    i. stimulating production of a leukotriene or a leukotriene  
25 leukotriene metabolite in a test sample from the individual, using a calcium ionophore;  
    ii. comparing the level of production of the leukotriene or  
leukotriene metabolite with a control level,  
wherein a level of production of the leukotriene or leukotriene  
metabolite that is significantly greater than the control level, is  
30 indicative of an increased risk of atherosclerosis.

170. The method of Claim 169, wherein a level of a leukotriene metabolite is compared, and the leukotriene metabolite is selected from the group consisting of: LTE4, LTD4 and LTB4.
- 5 171. The method of Claim 169, wherein the test sample comprises neutrophils.
172. A method of assessing an individual for an increased risk of stroke, transient ischemic attack, transient monocular blindness or  
10 asymptomatic carotid stenosis, comprising:
- i. stimulating production of a leukotriene or a leukotriene metabolite in a test sample from the individual, using a calcium ionophore;
  - ii. comparing the level of production of the leukotriene or a  
15 leukotriene metabolite with a control level,
- wherein a level of production of the leukotriene or leukotriene metabolite that is significantly greater than the control level, is indicative of an increased risk of stroke, transient ischemic attack, transient monocular blindness or asymptomatic carotid stenosis.
- 20 173. The method of Claim 172, wherein a level of a leukotriene metabolite is compared, and the leukotriene metabolite is selected from the group consisting of: LTE4, LTD4 and LTB4.
- 25 174. The method of Claim 172, wherein test sample comprises neutrophils.
175. A method of assessing an individual for an increased risk of PAOD, claudication, or limb ischemia, comprising:
- i. stimulating production of a leukotriene or a leukotriene  
30 metabolite in a test sample from the individual, using a calcium ionophore;

- ii. comparing the level of production of the leukotriene or leukotriene metabolite with a control level,  
wherein a level of production of the leukotriene or leukotriene metabolite that is significantly greater than the control level, is  
5 indicative of an increased risk of PAOD, claudication, or limb ischemia.
176. The method of Claim 175, wherein a level of a leukotriene metabolite is compared, and the leukotriene metabolite is selected from the group  
10 consisting of: LTE<sub>4</sub>, LTD<sub>4</sub> and LTB<sub>4</sub>.
177. The method of Claim 175, wherein test sample comprises neutrophils.
178. A method of assessing response to treatment with a leukotriene  
15 synthesis inhibitor by an individual in a target population, comprising:  
a) assessing the level of a leukotriene or leukotriene metabolite in the individual before treatment with a leukotriene synthesis inhibitor;  
b) assessing the level of the leukotriene or leukotriene metabolite  
20 in the individual during or after treatment with the leukotriene synthesis inhibitor;  
c) comparing the level of the leukotriene or leukotriene metabolite before treatment with the level of the leukotriene or leukotriene metabolite during or after treatment,  
25 wherein a level of the leukotriene or leukotriene metabolite during or after treatment that is significantly lower than the level of the leukotriene or leukotriene metabolite before treatment, is indicative of efficacy of treatment with the leukotriene synthesis inhibitor.
- 30 179. The method of Claim 106, wherein the level of the leukotriene in steps (a) and (b) is assessed by measurement of *ex vivo* production of the leukotriene in a sample from the individual.



180. A method of assessing response to treatment with a leukotriene synthesis inhibitor by an individual in a target population, comprising:
- a) stimulating production of a leukotriene or a leukotriene metabolite in a first test sample from the individual, using a calcium ionophore, before treatment with a leukotriene synthesis inhibitor;
  - b) stimulating production of a leukotriene or a leukotriene metabolite in a second test sample from the individual, using a calcium ionophore, during or after treatment with the leukotriene synthesis inhibitor;
  - c) comparing the level of production the leukotriene or leukotriene metabolite in the first test sample with the level of production of the leukotriene or leukotriene metabolite in the second test sample,
- wherein a level of the leukotriene or leukotriene metabolite in the second test sample that is significantly lower than the level of the leukotriene or leukotriene metabolite in the first test sample, is indicative of efficacy of treatment with the leukotriene synthesis inhibitor.
181. A method of assessing response to treatment with a leukotriene synthesis inhibitor, by an individual in a target population, comprising:
- a) assessing the level of an inflammatory marker in the individual before treatment with a leukotriene synthesis inhibitor;
  - b) assessing the level of the inflammatory marker in the individual during or after treatment with the leukotriene synthesis inhibitor;
  - c) comparing the level of the inflammatory marker before treatment with the level of the inflammatory marker during or after treatment,

wherein a level of the inflammatory marker during or after treatment that is significantly lower than the level of inflammatory marker before treatment, is indicative of efficacy of treatment with the leukotriene synthesis inhibitor.

- 5           182.   The method of Claim 181, wherein the inflammatory marker is selected from the group consisting of: C-reactive protein (CRP), serum amyloid A, fibrinogen, a leukotriene, a leukotriene metabolite (*e.g.*, cysteinyl leukotriene 1), interleukin-6, tissue necrosis factor-alpha, soluble vascular cell adhesion molecules (sVCAM), soluble  
10           intervascular adhesion molecules (sICAM), E-selectin, matrix metalloprotease type-1, matrix metalloprotease type-2, matrix metalloprotease type-3, matrix metalloprotease type-9, myeloperoxidase (MPO) and N-tyrosine.
- 15           183.   A method of preventing MI, stroke or PAOD, in an individual with an ankle/brachial index less than 0.9, comprising: administering a leukotriene synthesis inhibitor to the individual in need thereof, in a therapeutically effective amount.
- 20           184.   The method of Claim 183, wherein the individual has at least one risk factor selected from the group consisting of: an at-risk haplotype for myocardial infarction, stroke or PAOD; an at-risk haplotype in the FLAP gene; a polymorphism in a FLAP nucleic acid; and an at-risk polymorphism in the 5-LO gene promoter.
- 25           185.   The method of Claim 183, wherein the individual has at least one risk factor selected from the group consisting of: diabetes; hypertension; hypercholesterolemia; elevated triglycerides; elevated lp(a); obesity; ankle/brachial index (ABI) less than 0.9; and past or current smoker.
- 30           186.   The method of Claim 183, wherein the individual has at least one risk factor selected from the group consisting of: a transient ischemic

attack; transient monocular blindness; carotid endarterectomy; and asymptomatic carotid stenosis.

- 5           187.   The method of Claim 183, wherein the individual has at least one risk factor selected from the group consisting of: claudication, limb ischemia leading to gangrene, ulceration or amputation; and a revascularization procedure.
- 10           188.   The method of Claim 183, wherein the individual has an elevated inflammatory marker.
- 15           189.   The method of Claim 188, wherein the inflammatory marker is selected from the group consisting of: C-reactive protein (CRP), serum amyloid A, fibrinogen, a leukotriene, a leukotriene metabolite, interleukin-6, tissue necrosis factor-alpha, a soluble vascular cell adhesion molecule (sVCAM), a soluble intervascular adhesion molecule (sICAM), E-selectin, matrix metalloprotease type-1, matrix metalloprotease type-2, matrix metalloprotease type-3, matrix metalloprotease type-9, myeloperoxidase (MPO) and N-tyrosine.
- 20           190.   The method of Claim 183, wherein the individual has increased LDL cholesterol and/or decreased HDL cholesterol.
- 25           191.   The method of Claim 183, wherein the individual has increased leukotriene synthesis.
192.   The method of Claim 183, wherein the individual has had at least one previous myocardial infarction or ACS event, or has stable angina.
- 30           193.   The method of Claim 183, wherein the individual has had at least one previous transient ischemic attack, transient monocular blindness, or stroke.

194. The method of Claim 183, wherein the individual has asymptomatic carotid stenosis or has had a carotid endarterectomy.
- 5 195. The method of Claim 183, wherein the individual has had a revascularization procedure.
196. The method of Claim 183, wherein the individual has atherosclerosis or who requires treatment (e.g., angioplasty, stents, revascularization  
10 procedure) to restore blood flow in arteries.
197. The method of Claim 183, wherein the leukotriene synthesis inhibitor is selected from the group consisting of: 1-((4-chlorophenyl)methyl)-3-  
15 ((1,1-dimethylethyl)thio)-alpha,alpha-dimethyl-5-(2-quinolinylmethoxy)-1H-Indole-2-propanoic acid otherwise known as MK-0591, (R)-(+)-alpha-cyclopentyl-4-(2-quinolinylmethoxy)-Benzeneacetic acid otherwise known as BAY-x-1005, 3-(3-(1,1-dimethylethylthio-5-(quinoline-2-ylmethoxy)-1-(4-chloromethylphenyl)indole-2-yl)-2,2-dimethylpropionaldehyde oxime-  
20 0-2-acetic acid otherwise known as A-81834, optically pure enantiomers, salts, chemical derivatives, and analogues.
198. The method of Claim 183, wherein the leukotriene synthesis inhibitor is selected from the group consisting of: zileuton, atreleuton, 6-((3-  
25 fluoro-5-(tetrahydro-4-methoxy-2H-pyran-4yl)phenoxy)methyl)-1-methyl-2(1H)-quinolinone otherwise known as ZD-2138, 1-((4-chlorophenyl)methyl)-3-((1,1 dimethylethyl)thio)-alpha,alpha-dimethyl-5-(2-quinolinylmethoxy)-1H-Indole-2-propanoic acid otherwise known as MK-886, 4-(3-(4-(2-Methyl-imidazol-1-yl)-phenylsulfanyl)-phenyl)-tetrahydro-pyran-4-carboxylic acid amide  
30 otherwise known as CJ-13610, their optically pure enantiomers, salts, chemical derivatives, and analogues.

199. The method of Claim 183, wherein the leukotriene synthesis inhibitor is a FLAP inhibitor or antagonist.
- 5 200. The method of Claim 183, wherein the leukotriene synthesis inhibitor is a 5-LO inhibitor or antagonist.
201. The method of Claim 183, wherein the leukotriene synthesis inhibitor is a leukotriene inhibitor or antagonist, or an antibody to a leukotriene.
- 10 202. The method of Claim 183, wherein the leukotriene synthesis inhibitor is a leukotriene receptor inhibitor or antagonist.
203. The method of Claim 202, wherein the leukotriene receptor inhibitor or antagonist is an agent that inhibits or antagonizes a receptor selected from the group consisting of: BLT1, BLT2, CysLTR1, and CysLTR2.
- 15 204. The method of Claim 183, wherein the leukotriene synthesis inhibitor is an inhibitor of a member of the leukotriene biosynthesis pathway.
- 20 205. The method of Claim 204, wherein the member of the leukotriene biosynthesis pathway is selected from the group consisting of: FLAP, 5-LO, LTC4S, and LTA4H.

## ABSTRACT OF THE DISCLOSURE

5           Linkage of myocardial infarction (MI) and a locus on chromosome  
13q12 is disclosed. In particular, the FLAP gene within this locus is shown by  
genetic association analysis to be a susceptibility gene for MI and ACS, as  
well as stroke and PAOD. Pathway targeting for treatment and diagnostic  
10 applications in identifying those who are at risk of developing MI, ACS,  
stroke or PAOD, in particular are described.

15

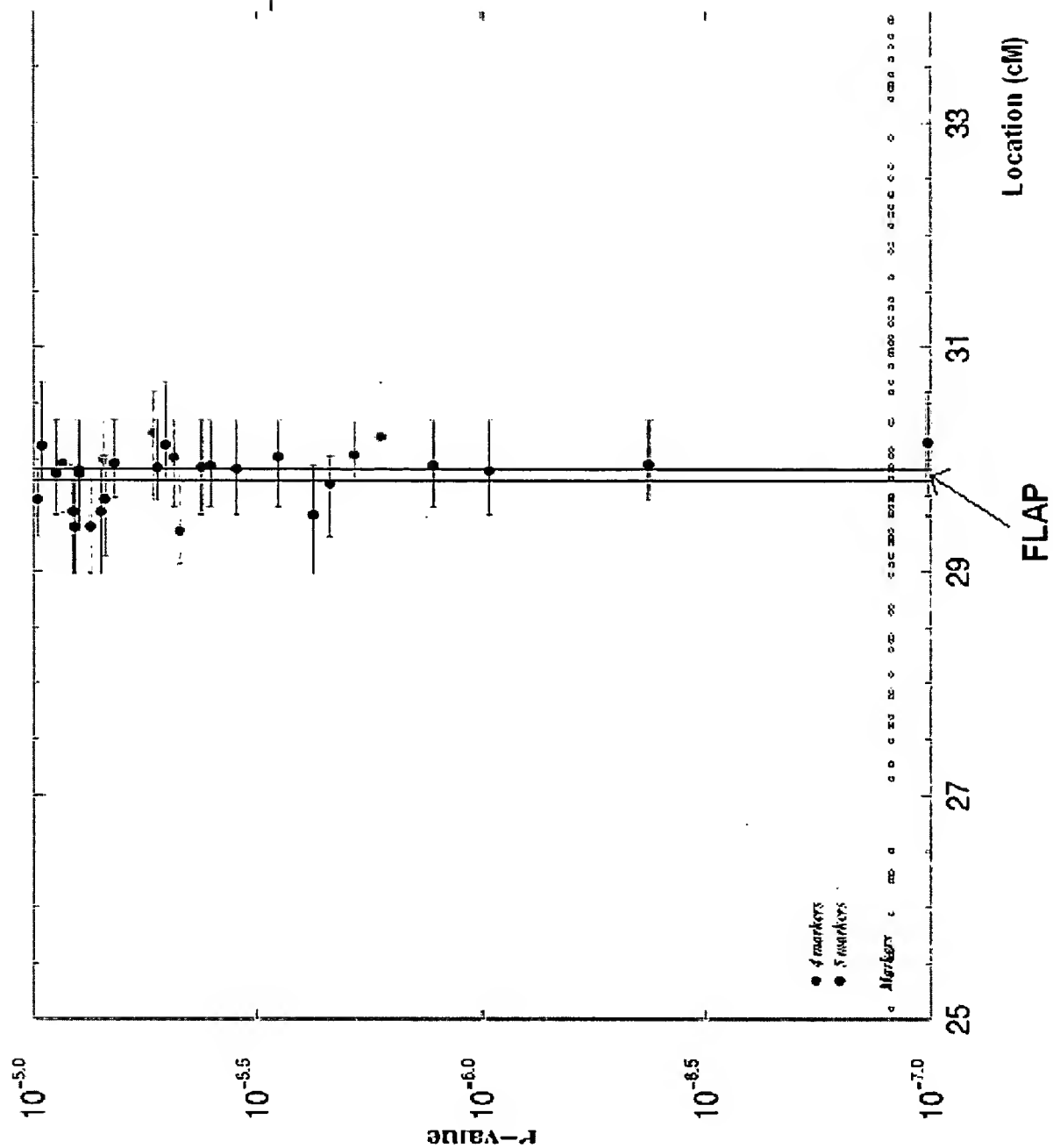


FIG. 1

Haplotypes showing association  
 (p value <  $10^{-5}$ ) with the disease

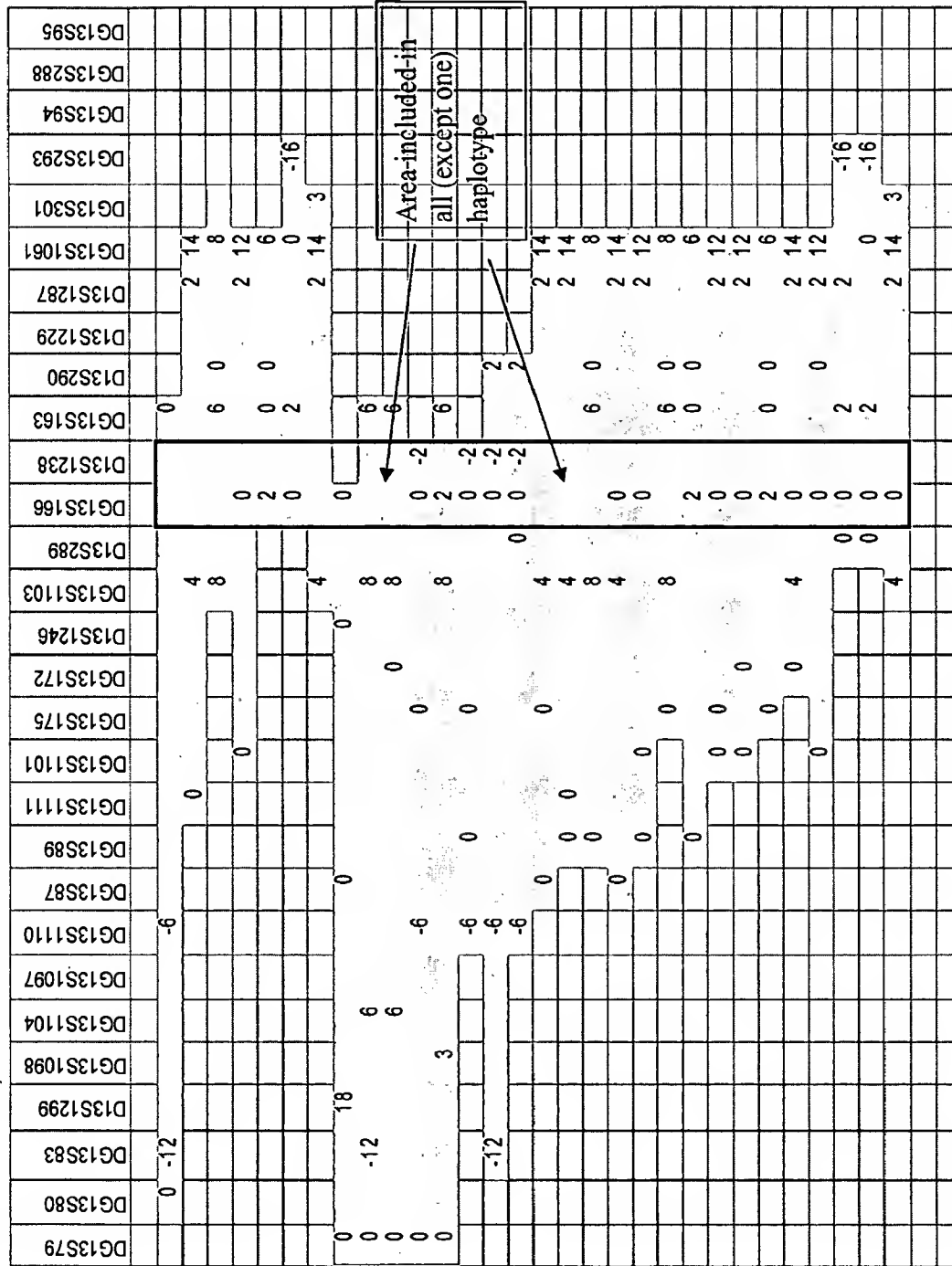


FIG. 2



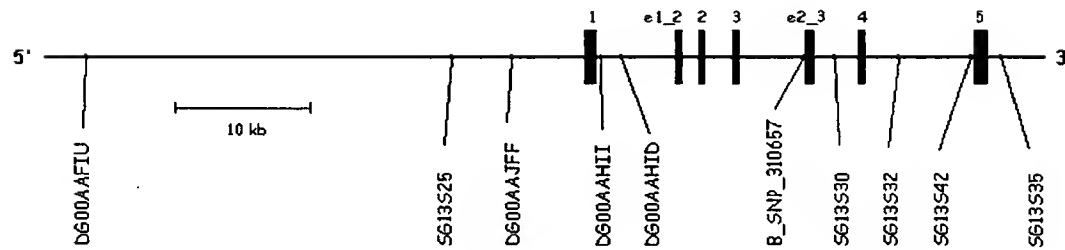


FIG. 3

Amino acid sequence of FLAP (>alox5ap\_protein translation NM\_01629)  
MDQETVGNVVLLAIVTLISVVQNGFFAHKVEHESRTQN  
GRSFQRTGTLAFERVYTANQNCVDA YPTFLAVLWSAGL  
LCSQVPAAFAGLMYLFVRQKYFVG YLGERTQSTPGYIFGK  
RIILFLFLMSVAGIFNYYLIFFFGSDFENYIKTISTTISPLLLIP  
(SEQ ID NO: 2)

MRNA of FLAP (NM\_001629\_mRNA)

Acttcccctctgtacagggcagggtgtgcagctggaggcagagcagtcctctctggggagcctgaagcaaacaatgg  
atcaagaaactgtaggcaatgtgtcctgttggccatcgtcaccctcatcagcgtgtccagaatggattcttggccataa  
agtggagcacgaaagcaggaccagaatgggaggagctccagaggaccggaacacttgcctttgagcgggtctaca  
ctgccaaaccagaactgtgtagatgcgtacccactttcctcgctgtgctctggtctgcggggctactttgcagccaagtcc  
tgctgcgtttgctggactgatgtacttgttgtgaggcaaaagtactttgtcggttacctaggagagagaacgcagagcacc  
cctggctacataatttgggaaacgcatactctcctgttcctcatgtccgttgcgtgcatattcaactattacctcatctctt  
tttcggaagtgaactttgaaaactacataaagacgatctccaccaccatctccctctacttctcattccctaactctctgctga  
atatgggggttggtgttctcatctaataacacctacaagtcataaattcagctcttgagagcattctgctctcttagatgg  
ctgtaaatctattggccatctgggcttcacagcttgagttaaccttgcctttccgggaacaaaatgatgtcatgtcagctccg  
ccccctgaacatgaccgtggccccaatttgcatttccatgcattttgttgttcttcaattatcctgttctctgaagatgttt  
gtgaccaggttgtgttttcttaaaataaaatgcagagacatgtttt (SEQ ID NO: 3)

FIG. 4

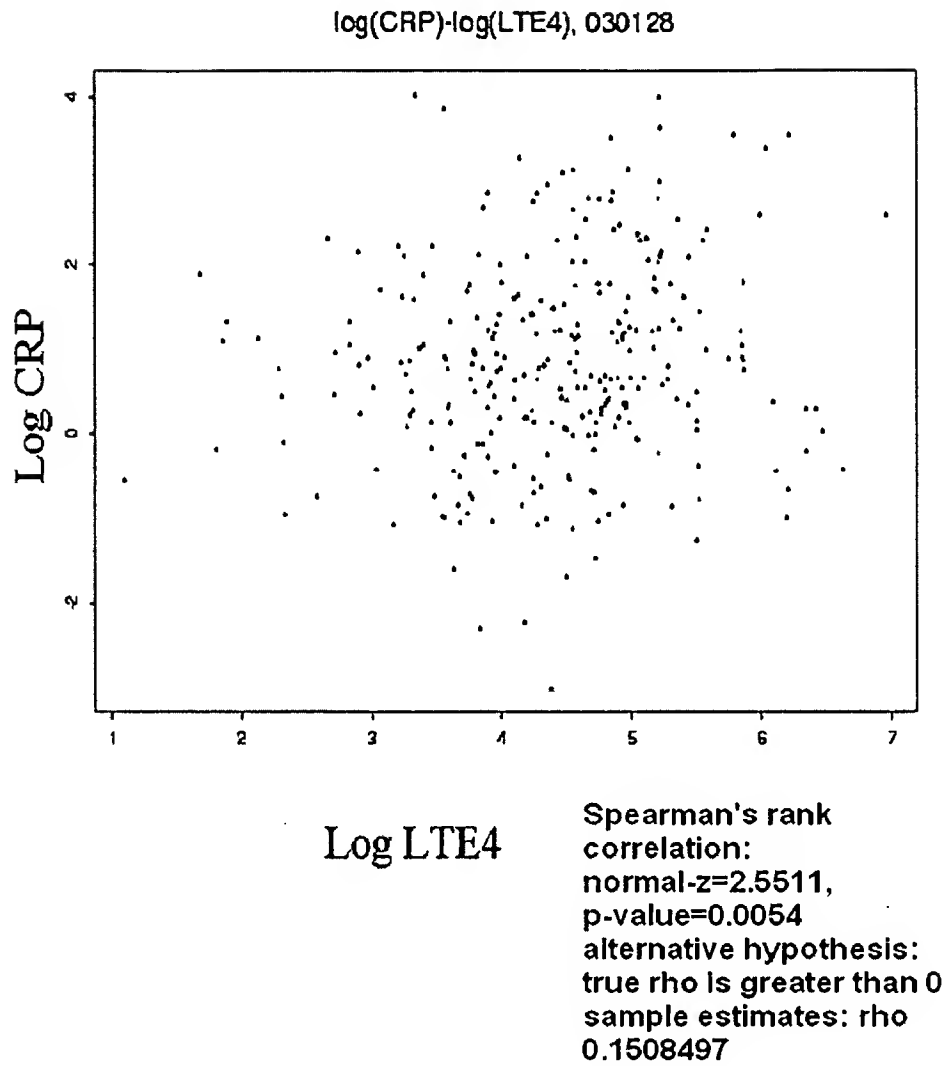


FIG. 5

ID CHROMOSOME 13: 28932001-29146000BP in NCBI build 34.

SQ Sequence 214000 BP SEQ ID NO: 1

```

GACTAAGATG AATATGCATT CATTACACAA AATCTCATAT TCCCAAAAAG CAGGAAAGGT      60
AGTACAGTGA GATGGATGAT GCCTTCACAT GACTCAGATG TCACGTGTTT CTCACCATTG      120
AGACCCCCAA GGCACCCCCT CCCAGCATTG ACCAGAATGT GTGTGTAAC TTTTACAGTG      180
ATTTGTGTAA TTATTTGATT GTTTCTCTTG TATCCTGTAG CAATGAGGGT AGAGATTATA      240
TCCCACCTAC CACTGCAGCT CCAGGATCCA GCTTCACAAA CATTTGTTGA ATGAATGAAT      300
AAGAAAAGAG GACACCCCCA AAGAGGCTGC AAGGGAAGAA GCTACAAAGA CAGAAGCACC      360
AGGAAAAAGT AGGGTCATGT AAGTCAAAGC AGGAAAAAAG TTCCATGGTG GGGTGGTCAG      420
CAGTGCTCTA TGCCACGAAG GCACAAAGTA GGATAAAGGT TAAAAATCAG CCTTTGGTTT      480
TGGCAAATAT GAAGCTTATC GGTAGCCTTA GCGAGAACAA TTCCATCAGG GAGCAGAAGC      540
TAACTGCAGT GGGTTGAGTC ATCAAGCAGG CATAAGGAAG TAGGGATACC CCATTATAAG      600
CTACTCTTTC AAGAAAGCTCA AATCTGAAGG TTAGGAGAAT TAGGTCAGTA GCTAGAAGGA      660
AATGTGGAGT CGAGGGGCTG TTTTCTCTCC CAAGGAGTAT AAAGGTGTAA CGTTGCATGA      720
AACCACCTTC GACAAAGGCC GATATCAATA GAGAAGTTAA AACGCACGCC TCAAGATTG      780
GGAAGGCTTG GGGTTGGGCT TAAAGAGGTA GGAGCATATT TCCTATCCTA GGACAGAGAA      840
TAAAGAAGAA AGGATAGGTT CCCATGGAGA TAAATTTCTA AGTGTTAAAG AAGAGGCTCA      900
GAAAATTCTA GCATGATAGG CTCACTTTTT TCTTTTTCCA TGAAGGAGAT GGCAAAGTCA      960
ACTGACATGA GAAAGGTGAC AATACTGATG GGTGAAGAG CGATGGACAT TTGAAATAAC      1020
TTCTTAGACC AGTAGAGGCT GGAGTTCATA AATCAGAACT GGCTACAGGT TATATATGTT      1080
TTTTTTTTTT TCTCCAACAG CATAAGATAA CAGAGCGAAG TCTGTAGAAA TGAAAGAAGA      1140
GTCAGATGAG GATAGCTGGA GCTAGTGCAA GGAGGGAAGC ACCACGGTGG GAGCCAGGTA      1200
CCCCCTGGAT TTATAATTCA TACTGAATTC CAACAACAGA AGGGCTCTAA GCAGGAGAGT      1260
GACAGATTTC AGAAGACTGA GACACATTTG GTAAAAAATA GTAGGAGGAA AACCTGATTC      1320
TGGAATTAGG GCAGCCAATA GACGGCAGTA TTTTCAGAAA GGAGGGAATG GTCAACAGTG      1380
ACTTTCTAGT CTGGAGCTCA GGAGGAAGAG GCAACTCTAC CTGATGGTAT TAAGATCATG      1440
GAGGTAGCTG AGATCACCTA GCTTGTGTGT GTCAAATGAG AAAAGAAGAA AGAATAGGAG      1500
AAGTTCCTCA GGAACACAGA CATTAAGTGG GGCTGTGGTG ACAACACAAG AAGAGAGGCT      1560
TGCAAAGGAG CCTGAGCAGC TGTCATGAGA GAGGTAGGAT GGTGGACTCG GAGAAGAGGC      1620
AGAAGATGTT CTTAAAGGAA GGACACTGCT GCCAAGTAGT CAGCCAATTG GTGACAAAGA      1680
AAGACCCTGT TGCGAGAAAA AAAGTCAGTG AAGTAGTAGG AACGATGACA GATGACACTG      1740
GGTTGAAGAC TGAGGAGAGA GAAGTGTAAG AGTGGAAGCA GAGGGCAGAC CACTCTTCTG      1800
AGACACTGAA GAGGCATAGT TAGAAATAAA GGGGAGTCGC CAGAAAGGAA TTTGTGGCTA      1860
AGCAAGAGGT TTTCTTTAAG ACTGAAATAC ATAAGCATGA TTAAATGCT GCTGGGATGG      1920
AGTTCACAGA CCTGGAAGAC AGAAGACAAA GCGGATCATC AAGATAGTGG AATTTACTGA      1980
AATGAGAGAG GAAAATCCCA TCCACAGGAA ATGCAGACAT GAGGGAGGGG CCAGAAGGAC      2040
AGTGAAAACA TCAGCAACTG GTCCCCCAAC TTCTGAGTGA ATGTGGAGAT ATAATCAGGT      2100
AAAGGACTGC ATCATCTCCC TGGTTAATGA TGGAGTCAGA GAAAAGAGTG TCTTATACAG      2160
AAGTTGTGAT AACTTGGCC GGGCGCAGTG GCTCACGCCT GTAATCTAAG CACTTTGGGA      2220
GGCCAAGGCA GGCGGATCAC CTGAGGTCAG GAGTTCATGA CTGGCCTGGT CAACATGGCA      2280
AAATCCCACC TCTACTAAAA ACAAAGCCT GTAATCCCAG CTACTAGGGA GGCTGAGGCA      2340
GGAGAATCGC TTGAACCCAG GAGGCAGAGG TTGCAGTGAG CCAAGGTCGC ACCACTGTAC      2400
TCCAGCCTGG GCAACAGAGC TAGACTCAGT CTCAAAAAAA AAAAAAAG ATGTATTTAT      2460

```

FIG. 6.1

TCTCACTGTA TAAATTTCTG TGTAAGAAAT ACTCTCTCAT ATAGAAGTAA ATTTATATAT 2520  
AAAATTATAT AGAACCACTA TAAAATACTC AGGTTTATAA AATTTATATA TAACTTGTT 2580  
GACATATAAA ATTCCATGTA AATGACTATA AAGTACTCTT ATATGAAAAG TATATGAATT 2640  
AAATTATATA TCAACTTACT TTTATATTAC AGTATTTTTG TTATACAGAA GTTTATATAG 2700  
TGACAATAAA TATTTCTCAA GAACGATTTC ACATAATAGA AGTATAAATT ATCCATTTCC 2760  
AATAGTGAAA AAGAAAAGCA GTTCCACACC AGTGACAGGG CTACGAATCT AAGAGGTACA 2820  
AAGACTTCAT TCTTAGAGAC ACTGAGGTCA GGGCATGGCC AACACATCTG AAGCTGATAG 2880  
AATTGGCGCT GGGTTGGTTG GAGACGGTAC GGTATTACTA TTACAATGGC AGACGCTTGG 2940  
CCTTGATAAC TAGCCAATCA GGGGGAAGA TTCTGGTTTC CTCTGTTATT ATCTGAAC TA 3000  
GTGTGTTCCC AAAGGGTTAA GATGTTTAT GGAAGGCACA AGATCAGCAA ACCATAAAGG 3060  
ATTAGCACTA AGAAGGAAGG AAGTAGACCA AGTGTTAATG GCGATGCCAT GTAAGAGCCA 3120  
GGTCTGCGAT GTATGTTCTA CATGGTTTGG GGGGTAAAAA AAATGTCAGC CTCCAGAGCA 3180  
CAGGGCTTTA AGCCTCAAGT ACTGTTAACA GTAGAGTTTA CTAGTCTACA GCAGGAATTA 3240  
CAACCAGTAA TTCTAAGGCC AATTACTCAG GCAAGTTTTA CTAGAACAAG GAAGCTCTGC 3300  
TTCGAGGTCA AATCGATTTC TGCATTTATA GAAGCATCTA GATGTTCTCT GTTCAAACAA 3360  
TGGGGTAAAA TCCCCACACA TTTTATTTCT GACAGAGTGT TCCCTATATT GCCTGGCCAG 3420  
GAGTGATAAC ATTGCTTGGC TATTATTAAT AAAACATTGC TGTGGCTGGG CGCAGTGGCT 3480  
CACACCTGTA ATCCTGGCAC TTTGGGAGGC TGAGGCAGGA GGATCACTTA ACTCCAGGAG 3540  
TTTGACAGCA GCCTGGGCAA CATAGCAAGA TCCCATCTCT CTAAAAAATT TTAAATTAG 3600  
CTGGGTGTGG TGGCAGACAC CTGTAGTCCC AGCTCCTCAG GAAGCTGAGG TGGGAGGATC 3660  
ACTTGAGCCC AAGCAGGTTG AGGCTGCAGC GTGCTGTGAC TGTGCCACTG CACTCCAGCC 3720  
TGCGCAACAC ACTGAGAGAG ACTCTGTCTC AAAAAAATAC ATCAAATAAA AATTTAAAGC 3780  
CCATTTCTTT CTTTTGGTAC ATTACAGCCA TGCACCTCAA AGGCTAGCAC AATTATTTTT 3840  
CTGCAGTTCT ATATTTAGAT TCTAGTTAGA AGTAACCTAG GACCTTCATG TTAGAGGTGT 3900  
CTTTGGCAAA ACTGTTATGT GAGTGAAACG TTTAATCAAT TGAGGATAAA GATGCCTCAT 3960  
TGCTAATGAA GATGTGGTTT AAGGATTTTA TGCACCCAGT TCATTTATTA ACAACTTGTT 4020  
TAAGCTTTAT TAGCTGGGTC TCTACTTTAT AACTGTGTTT TTTAATTTAC AAGACAATAA 4080  
AAATTAAAT GGTAATGGG AAACCTATCT TGCTTTTCAA TAAATAATTT ATTTTAATAA 4140  
CTTCGTGGGC ATGGTGGCCA AAACATTTTA GCTGTGAAAA TAATTTCAAT TCATATTTTT 4200  
TTGGAATCAA TATTTAAAGG TGATATATTC TCAAATGAAA AGTGGACAAA TGATCAGTTA 4260  
TAGGACATGA TTAAGAACT AACCATGAGC CACGTGCAGT GGCTCATGCC TGTAATCCCA 4320  
GCACTCTGGG AGGCCGCGGT GAGCGGATTG CTTGAGCCCA GGAGTTCAAG ACCAGGCTGG 4380  
GCAACATGGC AAAAACCCGG CTCTACTAAA AATGCAAAAA AAAAAAAAAA AAAAAAATT 4440  
TAGCTGGGTT TTGGTGGCTT ATGCCTGCAG TCCCAGCTAC TCGGGAGGCT GACTCGGGAG 4500  
GCTGAGGCAC AAGAATCATT TGAACCCAGG AGGCAGAGGT TGCAATGAGC TGAGAATACA 4560  
CCACTGCACT CCAGCCTGGG CAACAGAGAG AGAGAGACTC AGTCTCAAAA AACAAACAAA 4620  
CAACAAACA AACCGCTGCC CTGTGCTTGG AGAGATCTGT TTACCTTTAC CACTAAAGAC 4680  
TGTTGGAAGT AAATTTTAGA AGGTTTATAA TACCTAAAAG TAATCACTTC TGTCTTATGA 4740  
AAGGTTCTGC TGAGATTTTT CTATTGTGGC CACTAGTGGC AATATTCCAG AAGTCATATT 4800  
TAAAGAATAT CTTTAGTGGA TTCAGCAGTT TTTCAAATAT GTACTTTTAT CTCTCCAACA 4860  
TTCATGATTG CAATTTTCA AATTAACCTC ATGATATAAA CAACTGTACT CTATGATGCC 4920  
TCATAGTACA GAACTGGAG GCAGAAAGAG AAGTTGAATG TCTAAGAATC GGTAATTCTA 4980  
AAACTCAACA TAGACCATTG AGCATTAGTG GTTCTAACAA TCCCAGTCA AAATGAGTTG 5040  
ATAATGTGTA ACACTTTAGT GAACTAAAGC ATAAAGAACC ATGGTCTCCT AATGCAGCAA 5100

FIG. 6.2

ATTAACAC ATGATAGCTA CAATTAATGA AGTACATAGT CCTGGCTGGG CACTATGGTA 5160  
CGTCCTTTAC ATAGATTATC TCTTAAATTA TTAACCCCGT TTTAGAGATG AGAACATTCG 5220  
GGCTCAGGAA GGTTATGTAA GTTATATAAA AATCACAAAA TAAGAGACAG AGCTAAGATT 5280  
TGAATCCAAG TGTGACCAGG TTCATATCAA GCTTCCATTT TTGAATTTAT ATTAGAGGTC 5340  
AATAACTCAC CTTTGTCTT TTAATAAAT TTTTGGCTCT GTGACCTACA CAGGCAAGCT 5400  
GTTATTTACA AACAAACCCAC ACATCTAGAT GGTCACGTGTC TCACCGCCCA CTTTACCAT 5460  
CAGGACTCCT AGTGAGCTGT CAAGGGGAAT GCTATAATTT TGGAGGTTCT AAATCTGAGG 5520  
GCTTAAGAAA GAAAGAAAT GTAAAAAGCA GGCATTACTC AGGGGCATAG ATTGTCAGGC 5580  
AGATCTGTCA TGCTTATAGG TAACCTCCCA GGGCCAAAAA TATATGTGCC CAAACTGCCT 5640  
AAATATTTCC TGTCACTTCA TAATACTGCC TGAAATCCTG CCAAATTAGA ACTTCATTTG 5700  
TGTTGCTTGT CAATTTTAA CGCATAAGCA AATCACCTGG AGATCTTGTT AAAATGCAAA 5760  
TTCTGATTAG GTTAGGCTG GGTCTGCATG TCTGATATGC TTCCAGAGGG CACTGATGCT 5820  
GCTGGTCCAT GGACCACACT TAAAGAAGCA AAAAAGATGT CTGATATTTA CTCTCTGGCT 5880  
GCCTAGGAGT GCTTCTCATT TAAGTGAGAT CTCTTTGTGC ATCATAATGG GAGGGATGAG 5940  
CTGAAAAGCA GCAAATTAAG AGTGAGTTAA GTGTCTACCT CACTCCCTA CTATCTGTAA 6000  
CAAGCAGGTT TGGGCACTGT GGTCAACCAG AAAATTCTTT CCAGGACCAC AACCCTTGAG 6060  
ATTATGTTGC AAAGATGCAA GGACAACCTA GAAATAATTT CCAGCACTGG TGGCACTGGA 6120  
TGTCTGTGAG TGGTGCTGGT GGCAGGGTCC TATTCAGACT GTGGTTTACC TGCCTGGCCC 6180  
GTTTGTTTAT GGGCCATTTT CTGAGTACCA TGGAGCATCG CCCAGCTGAC AAGGGCTTGT 6240  
ACTCCACCCT TGGTGCGCAG AAGGGAAGCT TGGCTGCTAC TAAGTTTGGT GCAAAGTAAT 6300  
TGTGGTTTTG CCATTAATAT TTGATACAGT GAGTCCCTAC TTTCTCAGG TGAACTAGA 6360  
ACTTAAGGGG ACACGCTCAA GTTCTCATT TACAGTACTA AGTTTCAAAA ATCAGCAATT 6420  
TTATCAACA CATGCTCTAC AGCAGTGGTC GGCAAACCTT TTCTGTAAGG GGCCAGAGAG 6480  
TAAATGTTTT AGAGTTTCTG GGCCACATAT GGTTCCTGTT CCAGCTATAA ACTCTGCCAC 6540  
TGTAGGGCAA AAGCAACCCT CCACAATACA TACATGAATA GGTGTGTTCC AAAAAAATT 6600  
TATTTGTGGA CCCTGAAATT TGAATTTTCA AAACCTTTTCA TGTGTCATGA AATATTCTTT 6660  
TGATTTTTTC CCAACCTTTT AAAGATGTAA CAACCATTTT TAGCCTGTAG GCCATATAGA 6720  
AACAGGCAGT GGGCTGGGTT TGCTGACCCT TGCTCTGAAG CAATGATATC TCGATCCAAT 6780  
TTATACCCAC AAATTTTCT CTTGAAACC ATGCATTTAA TTCTCATCTC TTCTTACCAT 6840  
GACAATAAGA AGTTATTCTA TATAACAAAG AGATTGTACC CACCCAAGCC AGCATTTAGA 6900  
TCATGTGATT TGCTTCTCA AAATTTTGGT CTTTATAAAA ATCAATTAAA GCACCTTAAA 6960  
AGGTAAGCAG TGATGAAATA TTTGAAATAA TTGGCTAATT AAACATCACC TAAATAGAAA 7020  
CTGTGATAAG AACCACAAAT GCGAAAAGGA ATCATGTAGT AACTAATGTG GAGGATATCT 7080  
TGGTTTAGAG ATTTGATGAA CACGAGTTT GATTAAAAA AATTTGTGCA ATACTCACTG 7140  
CTTTGGTGGG GAGCTTGCTA TGCAAGTTGG TAGAAAAATT TATCCTAAAG TCACAGTTCT 7200  
CTACCACTCT GGATTTTCTC GAGCTAATA CCATTCCAAA CTATTTTAGG CACAGTTACT 7260  
AGTTTCAAGA ATCAGGCAAA TTGCCCTGGT ATTAGCACTG TTCTTTCTGT GGTCAACAAGT 7320  
CAAACACTG TGGTGAATAA AATTAGATGA TTTCTTTAGT CTTTCCTTT TCAGCCCCTG 7380  
TAGTCAATTT CCAGTGCTCC ATTCAAAGAA AAACCAAAAA TGTCCAGAAT ATAACCTTAT 7440  
TTTAAACTT GTTAACCACT GATTCACTT GTTAACCAAA TTTTTTTTTT TTTTTTTTTG 7500  
AGAATGAATC TCACTCTGTC ACCAGGCTGG AGTGCACTGG CATGATCTTG GTTCACTGCA 7560  
ACCTCCGCCT CCTGGGTAAT GGTTCAGCA ATTCTCCTGC CTCAGTCTCC CGAGTAGCTG 7620  
GGATTACAGG TGTGCACCCC CACACCCAGC TAATTTTTTT GTACTTTTAG TAGAGATGGG 7680  
GTTTACCAT GTTGGCCGGG CTAGTCTTAA ACTCCTGACC TCGTGATCCG CCCGCCTCGG 7740

FIG. 6.3

CCTCCCAAAG TGCTGGGATT GCAGGCATGA ACCACTGCGC CCAGCCTGTT AACCAAATTT 7800  
CTAATCACAC AACTTGAGG CCCAGTAAAT GCCTGCTGAA AAGAGGGTGC TGGTGGTGAG 7860  
GCAACTGAGG GGCTAACATA CTGATAGCTG CTGAAATCTT CTACAGCTCT TTCTTGTTAG 7920  
AACACTCCAT CACGGCTCCC AGGCCACAC CACATGAAGG AACTTCTAGC TCTCTTGCTT 7980  
GCTCTTTACC CAAATGTAGT TAGCAAGTCC TGGGAATAA ACAGCATTGA CACACTTGAA 8040  
GAAGACAATT AGGCAAATCC CAACTGCTGT GCTCCTGCAG CTAAAGATGA AGACTCGTCC 8100  
ATTGGGCAGT TGATTAATTG TACCTAGAAA ATTAATTTCA ATGGTCCCAT GACAACATAC 8160  
GGGCAGTGAA GCTCTAGTGT TCCCCCTGGG TGAATCTTC CAGGATGTAT AGTCTCCCAT 8220  
ACCAGCTCAT CCTCCATT TTCCAGATTC TGGTTCTTCT CTCTTACCTA GTGTGTAGTG 8280  
GGCCAAATGG TGGTCCCCCA AAAAGATATG TCCATGTGTT AACCTGGAA ACTGTGGATG 8340  
TAACCTTATT TGGAAAAATG GGGCCAGGTG CAGTGGTGTG CATGTGTAGT CCCAGAACTT 8400  
TGAGAAGCCA AGGTGGGAGA ATCGTTGGAG CCCAGGAGTT CAAGAACAGC CCAGGCAACA 8460  
TATTGAGACC CCCGTCTCTA TAAGCAATAA AAAATTAGCT AGGTGTGGTG GCATGCACCT 8520  
GAAGTTCCAG CTACTTGAGA GGCTGAGGCA GAAGGACTGC TCAAGCCCA GGAGTTCAAAG 8580  
GCTGCAGTGA GCTATGATCA TGTCACCCCA CTCCAGCCTG GGTGACAGAG TCAGACTCCC 8640  
TGTCTCAGGA GAAAAGAAAA AAAGGTCTTT GTAAATGTAA TAAAGAATCT TGAGATAAGA 8700  
TCATCCTGAT TTAGGATGGA CCCTAAATCC AATGACATTT GTCCTTACAA AAGAAAGGTA 8760  
GAGGGAAGT TGAGACAGAC ACAGAGGGGA GGGCCTTGTG AAGCAGGAAG CATAGATGCA 8820  
GTTACAAGTC AAGGAATGCC AAGGACTGTC TACAACCAGA AGCCAGGAGA GATGCATGGG 8880  
ATGATTTCTC CCTCACAGCC TCCAGAACTT CTGGCCTCCA GGACTGTGAA GAATCAATTT 8940  
CTGTTGTTTT AAGCCACCAA GTTTGTGTGT CATTGTAT GGCAATGGCA GTATTAGGAC 9000  
TCTAATACAC AGTATAAAAA AATAAAAAATA GGGCCAGGCG TGGTGGCTCA GACCTATAAC 9060  
CCCAGCACTT TGGGAGGCTA AGGCGGGGAG ATCACTTGAG GTCAGGAGTT TGAGACCAAC 9120  
CAGGCCAACA TGGTGAAACC CCATCTCTAT TAAAAATAA AATTAGTTGG GCATGGTGGT 9180  
GTGCATCTGT AATCCCAGTT ACTCAGGAGG CTGAGGCAGA AGAATCGCTT GAACCCAGGA 9240  
AGTGGAGGTT GTAGTGAATG CCACTGCACT CCAGCCTGGG TGACAGAGCT AGACTCCTTC 9300  
ATCCTAGGAC ACAGCCAAGT CTTACGTAGC AAAAGAAGT TGTTAAAGGT CTGTAGTTCT 9360  
GCATTAAGCA ACACAGGCAT GTACCTATGA ATTATATGAT TATAAAGTG CTCGGACAGG 9420  
CCCATTTCAA ACTTGGCCTC TTTCCACCA CTGTGTAAGT TTTCTCATT CATAACTAGA 9480  
GATTATGTCT TTATATCTG TCAAAAAAGT GAATTTTGT GGGCTAAGAC ATTATCCCTG 9540  
TGTTAAATGC ACCAGTCTTA GTGTAAACAA GCCTAGTTCC TTTTTCATT TGGCTGTCTA 9600  
GTATGCATTT GTATATGCTA GGCAGTGTAC TAGGCACCTT AAATACATTA CCTTGTTTAA 9660  
CCTCTACAGG ATTCTGGGAG GTAGGCATTA TCCCCATTT ATAGATGAGA AACTGAGAA 9720  
GACAATGTTC ATAAGTGGT CACTTGTCTG AGATGACATA TTTACTAAGT AGCAGAACCA 9780  
GGCCTCGAGC TACTCAGTCT GATTTCCAAA GCCCCTGCTC TTAATCACAT CAACTTCTTT 9840  
CCTATATCAC CTTTCCCAGA GTGCGCTCTC ATGGATAAAG AGCAGAAGTA TAAGTTACTA 9900  
GGCAGCAGAA AACTGTAGAG GTGGGAAGAT TAGATAAAAA ATGTAAATAA GAAGGCTTTA 9960  
AGACACCAAA ATCAAATGTA AATACTTTAT AACCTGAATC AGTGCTTGTG TTCATGAGGC 10020  
TAGAGGTCGT GCATTTTATC TCTAGGTCTG GTGATGCCAA TCCTGATCTA CAGCCAGCAG 10080  
CAACAGTTCC CTAGCCTGCC TAGAAGTTTG TAAATGCATG GGCTTTGGTA GGAGGAAGAC 10140  
GAGAGAAAGC AGAACAGATT ATTACAAACC CAGTGCATTC CCCCTTGATG GGTCACAGC 10200  
GATTTCTTTG TAAGTGAAGG ACAGCACACT GGTTTTGATG ACTCACGAGA GAGTAGGAGG 10260  
GAAAAAGAAG TCTGAGGCAT TGCCTGGAAG CCTCGCTCTG CTAAACAAG TACACTAATG 10320  
GCTCATGCCT GTTACTCCCA GCACTTTGGA AGGCCAAGAT GGGTGGATCA CTTGAGGCCA 10380

FIG. 6.4

GGAGTTTAAG CCCAGCCTGG TCAACATAGC GAGACCTTTT CTCTATTTAA AATAAAGAAG 10440  
AAAGAAAGTA ATAATGATT C AAGTTCTCAT TCTCTACAAA ATTCACCTAT GACTTTCCAA 10500  
ATGCTAGTGA AAACCTTTAG GTATTGCAAA ACTGCCTTAA TGCATAACGG GATTCTCATT 10560  
TACTTAGTTC TAAGATGACT TTTTCACTTT GAACTTCTGC ATCTTTATGA TCGCTTAGCT 10620  
TTCTGACAAG CAATTTCACT AAGTGTCTT CAATTTGCAT CCACACGCTG ACACATAGGG 10680  
GTCTACTTAC ATATCCTTCA TGTAAATTGAG CTTTGTGAAA TCATCTTTCT ACATGGTACA 10740  
CTTCTGATTT TGTGTGCAGC TTTCTTGTG AAGCACTGTA TTAAATGCTC TGCTTCCTAC 10800  
ACCTTAGGA ACAATGAGAA TAAAGCGTA ATGTTGGTTA CTTCTTCATA TCAAAGGAAG 10860  
TTCATCTCCT GGTATTAAA AGCTATTATT AAATGGCCAT CTTTTGTGC CCCTGTGTTA 10920  
AGCACTCTAC CAAGATACCA TTAAATAGAT AAGGGCCACA CTCCATAGAG ATGATGGTTC 10980  
TATATTCTGT ATTTTCTGGG GGAGTTCTAA TTTCATGCAA TTCCTTCTTC TTAAATAAAG 11040  
GCAATTCTCT AAATATATTA CCTAATGTGC TTTCACTTTC ATATTCTTGT AAGATTTTTC 11100  
ACATAAATCA ATTCTCAAAA AATAGTATCA TAGGCCTTTT AAAAATAGTC ATGTTCAAAA 11160  
GTCAGGCTCA TGAATAAATG TGTGCATTCA TTACATATAT TTCATAAAT TCAAATTTAA 11220  
AAGAATAAGA GTAGCTAGAA GGTGGAAGAA AAATCTTATT CTGATTAGGA ATGCACAATC 11280  
ACAAGAAAAT TTGTGATATA TATAGTCATT TTATTCTGTA TTGTTTTATT TTGATTTTGG 11340  
TAAGACAAGA AACAATGTAG AAAGTTTGAC AACTTAAAAA AGTAATATGA GTGTGAGAAA 11400  
GTCCTCTTCC AGGATTAGCA AAAAAATGGT TTTTTTTTTT TTTTTTCCG AGATGGAGTC 11460  
TCGCTCTCTC GCCCAGGCTG GAGTGCAGTG GCGCAATCTT GGCTCACTGC AACCTCCGCC 11520  
TCCCGGGTTC AGGTGATTCT CTTGCCTCAG CCTCCCAAGT AGCTGGGACT ACAGGCATGT 11580  
GCCACCATGC CCGGCTAATT TTTTTATTT TTAGTAGAGA CGGGGTTC CAATGCTGGC 11640  
CAGGCTGGTC TTGAACCTCT GACCTTGTA TCTGCCCGCC TTAGCCTCCC AAAGTGCTGG 11700  
GATTACAGGC GTGAGCCACC GTACCCAGCC TAAATGGCCA AGTTTTATTA TGGACAATTA 11760  
AGCTGTAGAA TAAAAATCTA CTTTAAATAG CTGGCATAGT GCCTAGTGGT TTTGAAGCCA 11820  
CAAGCAGGTT TACAAAAAC ATTTAAATCC ATCTGAATCT ACAGAAAACT AAGATTACCT 11880  
AAGCAGAAAA TGAATAATAG TCAGGATTAA GGAAGATTAA CAAATGAAGA GTATATGTAT 11940  
TTTAGAAGTA TACTTTATA TTTTATAGT ATAATAATAA TATTTACGTT CCTACACTTA 12000  
TAATGAGTTT CGTATATATA TTAAATAAT TTAATGGATT AGTATGTTA TATTTGCTT 12060  
TAGTAAATTT GGTGTATGAT AAACCTCAGT GTCTACATTG TGAGACTACA CCTGAGGCAA 12120  
TTTCTGTGTT GATATATACC TGAATAGCAG ATATTACTTG GGAGCAAATA AAATAGCTTC 12180  
AGGCCTAATT TTGCAAGTTC ATGATGGGAG AGTAAGCATG ACTTCAAAGA ACTGACTTTG 12240  
AGTTAAACT TGAAGAATGA ATGTGACAAC AGCAAGTATA AAACAATGCC AGGCAGAGGT 12300  
GGGACTGTTT ATGGGTATCA GGGTAAGTGT GTTGATAAAT GCTCAAAGTA GGAAATACCT 12360  
TTCTTCCCC ACACATGTCA GAAAATAACT GCAATAGAAT GCAACGACAT CTCAGAGATA 12420  
AAGTGTTCAA CTTAGCTCTC AGAGACCGTT CAGTTACATT TTGTAATGAC ATTGGAATTG 12480  
ATTGCATTTT GAAGGCAATT CTAATGCAA AGTCTTCATT TTGTTGATAG AAGCTGGGTT 12540  
ATTTATTATG AAATTTCAA AATTAAGTAA AATATCTAAT TAGGATTATA CCAGCAAAGG 12600  
CAAATTTAGA ATTCAAGACT TCATGATCCA TGGTAAGATT ATTTAATGC AACTCTGCTA 12660  
ATTAAGTAA ATTTCTTTA ACTCTCACAT CTGCCTTTA CTTCTTAAGA CATTTTCTA 12720  
GTATTTTACC AGAGCAAGAT ATCAGAAGGG TAAATCTCTT ACCAATGAAC TTTGCTAATT 12780  
CTTAGTGAAT CCGTTGACCC TGGTGTAAGG ATCAGGAACA AAGTGAATGA AATACATTTT 12840  
AATACATTTT TGCTTTCTCT AATTCCAAAG ACCACTCTAA AGAATAAGTT ATTTGTGGGT 12900  
ATTATCTGAA ACTTGGGATT AAAAGAGACC GTGATTACCC TTCAGGGATT TTGGCAAAAC 12960  
TTAAGCCATT TCATCTGAAG AGCAAAGCAA GCCTCCACA CTCTGGCTT ATTCTCACA 13020

FIG. 6.5



TTATCTAGAT ATCTAGCAAC AAAACTCTTG AGTAGTTTGT TAACTACAGA TGCCAAGGGC 13080  
TGACAGTTTC ACTTTCAGTT TTCAGAATAT CTTTTGTTTC AGTGGTGTAA GCACACCATC 13140  
AGAATCTCTA CTATTTAAAA TAATTAAGTT ATAATTGTAA CTTCCATTAG ATGTAGTACT 13200  
TAAAGGAATC TAGAAGACAC AACTCATTAA TTATAGGAAT TTGACTGCAA ATTCTTCTGG 13260  
GGGGTCTGAA TTGCAAAGGA GGCATCTTTG TAAGTCAGAC TCAACTCATT ACTCTGTGAT 13320  
GCAGGCTCCT CCAAATGGCA GCAGAAACGT ATTACTCTCT AGAAACACTA CAGTAGTGCT 13380  
ACAATTTTCTAG GGTCTGTAG AGATAAGGAC AAATTGACAG AAACACATTC TTAGAAGGAC 13440  
AGTATCATTT AAAATAAAAA TACTGTCATA ATTGTACACC AGGATAGCTT CTCCATAATA 13500  
AATTCTTTAT GATTTTCTGA TTTTGTAGAA TCAGAATTGA ACTTTTAAAT GTGAAAAAAA 13560  
TGAGAGAATT GTTTCAAAAT AGGACCACAT TTCTGTGTAT AATTTTAAAA GTTTAAAAAT 13620  
ATTTGATTAG TAGACTGATA AACTGAAACA TTTTGTAGAA GCTTTTCATT ACATACAAAC 13680  
CATATAATTT GTAAAAAATT GGAAATTATT CAAAACCTCA CATAACTAAA GTGACCAAAT 13740  
AAATACTGGA GAGGAAAGAA AAGGAGTCAA ATGAATCTAG CATTCTCTTT TTTTTTTTTT 13800  
TTTTGGAGAA AGGGTCTCAC TGTGCCACCC AGGTGGGAGT GCAATGGCAC GATCATGGCT 13860  
CACTGCAGCC TCAACTTTAT GGGCTTAGGT GATCCTCCCA CCTCGGCCCTC CCAAGTAGCA 13920  
GGGACTACAG GCATGCGCCA ACACGTCCAG CTAATTTTTT TGGTATTTTT TGCAGAGACG 13980  
AGGTTTCACC AGGTTGCCGT GGCTGATCTG GAACTCCTGG TCTCAAGTGA TCTACCCAAC 14040  
TCAGCCTCCC AAAGTGCTGG GATTACAGGC GTGAGCCACC GCACCCGGCC TAATCTAGCA 14100  
TTTTCTAAAA GGAAGGACCC AGCAGTGAAC GGCAATATCA ATAATCATGT TCAAGACTAT 14160  
CAGACATGCA AGCTGGGGAT GAATGGGTGG AAGGGGAAAA TGATGAATAA ATGATGAACA 14220  
CAAGTATAGA CCCAGTGGAT TTGAGATGCC CAAGATGCCA GTGAGATATT CAAAGTTTAA 14280  
CTCAAAAGCC ACTTCCCATA TGAAATCCTG ACAAACACTC CTACGTCCAA CTGGAATTAA 14340  
TTTCTCTTCT GGGCTCCAC AGCACTCTGT ATTTTCTAA TAGCATAACA CTATTTTGTT 14400  
TGATGATATT TCTCTGATAG CATTACTATC TTTCTCTTT ATCACAACCTG TTTGAAGTTC 14460  
TTTTGCCTCT TGCATCCACT GTTGCCCAAT CCCACTGCTG GAAGGCTCAT CTTATTAAGT 14520  
TCTGTATTCC TAGTGCTAAC ACACTGTCTA CCATAGATGA TGTTCAATAA ATGTTTGCTA 14580  
AATGAATTCT CTTGTGATAA TAGCACTATG GCAACATAAT CGACGGTAAA AATTCTTCT 14640  
CAATGTTTAC TTTTAGCAGA ATGCATTCAT TTATCAACTT TCATTGAGAA TATGCTAATT 14700  
TCCATGACCC TGCTAGGAAA TAGGAAAATA AAGATGAATG TAATAAGGTG CTCATTCTAC 14760  
TGAAAGTCTT GACTAGTGA GAATTATGGA TCCAACCTTT CATGAAATGC CTTCACTGGT 14820  
AAGAATTCTC ATATTTGGAA TAAAAATGT TATGGGTTGT GCCAAGATAC CTACATACTT 14880  
CATAATTTTG TAGAGGGCTG TCCTTACTGC AGAAATGTAT ACTACTATAG TCATATGTGG 14940  
AAATTCTTTT TATGATGCTA ACTGCATGCT AACCAGACTT TTTAATTTAA TACTTGCATT 15000  
AAATAAACCA TGCTAGGAAT CCAGGAATCT AGCTTGGTTT ATTTTCCATA CAATGTACTC 15060  
TTTGTAATAT GCATATACTA CATAAAAT CTATTAATGG CCTCGTACTA AAGATGTGTC 15120  
TGTTGGGGAA TCAGTTATTC TGTATAATTT TATCTTAATT GATATATTAA AATCTACCAA 15180  
AAATATAAAC TCCGAGTAAA AGTATCTGCA TGGTGTGCAT ATGTTTATTA TTTAAGTGT 15240  
CAGCGTATAC ATTTTCATGC CATAAAGTTA TAAATGAAA AAATAGTAGC CTTTTATATT 15300  
AAGTTCATGC TTATGTAGTT AGTAAAAACA AGAAAGCAAT TAACATACAA ACCATGATGG 15360  
TGGTTAACT TGCTTCAGTT TGTGTTTTTT AAAATTTGAA AGTGAGAAAT ACAGCTCGAA 15420  
GTCAGCTCAT ATTTTCAGTA AGTACTGATG AGGATGTACT GGCCCTATTG ACTACGCTGA 15480  
CCCCATTTAA ATATTTGTGA GTCTAAAGGT TCATATGACG CTGTTCTTCT ACTCTAGCAA 15540  
CAGGCCATAC ATGTCTTACA TAGGGACTCT GTTCAATTCA TTAATACCTC CTGAAGTGCT 15600  
CAACATCGTG GTTCATTTAT AGTAGATACT CAATACATAC TCCATTAAT GAATTCTAAG 15660

FIG. 6.6

ATAAACTGTC TGTTACTGAC AGAAATTTTC ACTTAAGGGA GTCTCCGTGG CTGAAGGCAA 15720  
TTTTGAAATC CTGTAAAAGA ACCCACTCCT CTCCCCAAGT AATGAAGTTT GTCAGTTTCA 15780  
AGCCTGTAAT AAGGTAAGTGA CTTAAATTA ATTTTCTAAT AATACAGTAC TGCTATGTAT 15840  
CTAATGTGGG GTTAGTCAAT GATAGGAAAA AAACATAAGA CAGAGTCACA TTTAAAAATG 15900  
TGTGCTTAGG TGCATGGTGA CACCTGCCTG TAGTCCAGCT ATTCCAGGGG CTGAGGCAGG 15960  
AAGATCCCTT GAGCTCACGA GTTTGAGGCT GCAGTAAGCC ACTGCACTCA GCCTGGGCAA 16020  
CAGAGTGAGA CCCTGTCTCT AAAAAAATT CGTTTTAAGT GTGCTCAGGA CATAACAGGA 16080  
GCCGCTGGTA ACATGCCATT TCCACTGTGA ATATGGTAAG GACAGAATCC CTGTCTCTAG 16140  
GCCCTCTCC ACTAGTCAAT CTCATCATCA CCATCAAGGC CAACATTGGT ATTCTCTCCT 16200  
CTGAGACAAA GTCTTTGACA TTTTCTATAC TATACTATGT CTTCTCTCC CCAAATGCAT 16260  
ATACAAATAA AATTGTAATG CTTCTTTCTC CATTTAGTGT AATTTTTTTT ATAACATAGA 16320  
CCCAATTTTC AAACCCACACA ATGGTGGATT TTATTTGATG TATTGTAAAA AGCGCTGGAT 16380  
TGAAGTCAAA TGGCTTGGGA GACCTAAATT CTA CTCTCTGC CTGTACCATG AAAGAGACAA 16440  
ATCCCAAGGC TTTGCAGGGC TTCAGCTTCC TTGTTTGTAG AATAAAGAAT TATAAAATCA 16500  
TCTCTTTTGG TCCTACTGGG CAATAAAAAG CTATGATTCT AAGCCTGTTT CCTTTTCTCA 16560  
CCTAAGAATA CAAATTTGAT ACAAAGAGGC CGCAGAAATGT GTCAAACACT CCCTGTTGCC 16620  
TGGAATTCTC TCTTCTTTG GGTTTCAGGGA TAAAGGTATG TTATTTCTTA AGTCTCCCTT 16680  
TGCTTTCTTC TGCTTGCTC GTAAATATTT TTCCATCTTG GCAGTCCTAC ATGTCTTCTC 16740  
ACTCTACATG TTTTCCCTAG GTGATGTGAC CCAGCCTGTG GCTTCCACTG CCATCCACAC 16800  
ACGTCGCTGC CTCTCTCCAC ATCAGCATCG CAACTATCTC CTGGAAGCTT TCCAAGTGCT 16860  
GAACTACAGT AACCTCAACC GAACTGCTGT TCATTCAACC CACAGGCTTG CCCCTCCTCT 16920  
GCATCTTTGT GAGAACCTGA GAGTCATCCT AAACCTCTCC TTCCACCTCA CTCCCCACAT 16980  
CAAATCGATT ACCAACTTGT GCTGATTTTA TCTTCAAATA CTCTCCAGAA TTGTCGCTGT 17040  
CATGGACTGA ATATTTGTGT TCCCCCAAAT TCATATGTCC TAATCCCTGA TGTGACTGTA 17100  
TTTAGAGACG TGACCTCTAA GGAGTAATTA AGGTTCAAGT AGGTCAAAGG TGGAGCCCTG 17160  
ATCTGATAGG ATCAGTGTCC TTATAAGAAG AGACTAGAGC TGGGCACAGG GGCTCACACC 17220  
TGTAATCCCA GTATTTTGGG AGGCTGAGGT GGAAGATCA CTCAAGGAGA GGAGTCTGAG 17280  
ACCAGCCTGG GCAACAGAGT GAGACTCCAT CTCTACAAGA AAATAAAATA GTCAGACACA 17340  
GTGGTACACA CCTGTGGTCC CAGCTCCTCA GGAGGCTGAG GCAGGAGGAT GGCTTGAGCC 17400  
CAGGAATTTG AGGCTGCAGC AAGCTATGAT CACACCTCTG CACTCCAGCC TGGGTGACAG 17460  
CATGAGACCC AGTCTCTTTA AAAAAAAAAA AAAAAAAGGC CATATATAGC CCAGAAGAGC 17520  
GTCCTCACCA AAACCCAATC CTGATAGCAC CTGGAGGACT TCCAGCCTCC AGAGCTGTGA 17580  
GAAAATTTCT GTTGCTTGCA CCGCCAGTC TGTGGTATTT TGCTGTGGCA GCCCAAGCTG 17640  
ACTCATCAGT GACCTTCTCT CTGTTACCGC AGAGTAGCTC ATCATCCTCT CTTCCCTAGA 17700  
GTCCAGCCAC TCTCTACAT CTACCTACCT AGCAGTATCA CTGTGGGTTA GAGTCAGATC 17760  
ACTGCGGATT AAGTCCTCAT TCTGCCACTG CCTGTGTAAG TCTGAGCAAG TTA CTTAATC 17820  
TCTCTGTGTG TCAGTAACCT CCCTGTGAAA TGAGGCTAAT AATAGCAGGG TTGTTTCAAC 17880  
AAGGCGATAC ATGCATAATG CTTACAACAC AGCTTGGCAC ATTATAAGCA TTCAACGAAA 17940  
AGTGAGCTAC TATTATCTCA TCCGTTATCA GAATAAACCA CCTAAGCCAC AAGGCTGCCC 18000  
ACATCATCCT CATGTTTTAA AACACTTCAG TGGGCTCCCC ACCATCAACA GGATAAAGTC 18060  
CAAGCTTCCT TAGCATTCTT TAGAGGCTCC ATATGAATCC CCAAGTTCCA CTACAGGAAC 18120  
ACAGGTGAAC TTCCACTCC AACCTCAGGC TCCTCGTGT CACTCCTCAT CCACATGGAG 18180  
GTAAGCAGCA AGAGACTCCG TGCAGTTCTT GGTGTTCCC TGACCCTCAG GCAGACTCTC 18240  
CCCAGCCCTC TGCCTGCAAC GTCCTTGCCC TTTGCTTCCC TTGGCCAGCT CCCATTCAAT 18300

FIG. 6.7

CTCCTTGATT CTGCTTGGAA GTTTCCTCT CAGGAAGGCT TTATGAACCT TAGTGTAGGT 18360  
TATGAACCCA TCTTTGCTCC TTTCATACCT TTGCAAGCC TTTATTTATT ATGACACTTA 18420  
ACCATTATCA TACTGAAGTG ACCTGTTGGT GTGTCTTTGT TCCCCACTAG ACAGAAAAC 18480  
CAAGATCAGA GACCAGTTCT TGTCTTTTT TTTTTTTTT TTTTTTTTT TTGTATCACA 18540  
GTGTTTAGCA GCCTGCTATA TGGTAAATGT CAGTAAATGT TCCACAACT GAATGGAATT 18600  
GAGCTCTGGA ATCTAGACCA TCTTTCCAT ACCCATCACT CCTGTCTTAG TTGAAGTCCT 18660  
TATTTCCCAT TTGAAGCAAT GCAAAGGATT TCCTAACTCT AATCTCTCTT TTCTTCACAC 18720  
CATCCTTTAA ACAGCCGACA GAATGGTCAT CCTAAAGCAC ATATATCCTA TCTTACATAT 18780  
CCTAGATTCG GAACCTCTCT GGGCTTCTCA CCATATAAGA AGAAAGTCTA ACCTCCTTAG 18840  
CAAGGTGCAT AGGTCTTCAA TGGGCTCCAC CTCACCTCTC TATATATACC TATACTCTTG 18900  
CTACACTAAA CTTCTTTCTT ACTGTTGCTG GAACAAGTTC AACGCTTTC AACCTCCCTG 18960  
ACTTTGCATA TGCAGTTCAT TCTGTCAGGA ATGCCCTTCT CTCTTATGCC TGGGATATTC 19020  
TCATTCATTC CATATGACCT ATTTCAATAAG TCACTCCTTA ATGAAGCCTT TCTTAGATAT 19080  
CCTACTGGGGC AATCAGCTGC TTGCTCCTGT TTCCACAGCA CATTGTTTAC ACAGATAGCA 19140  
CAGGACTTAC CACAAGTTAT TATAATTTTG TCTGTCTTGC CCATTTGAAT CCAAGGGCAA 19200  
GGACGGAATC ATTCTCATCT TTGTATGTCC TGGGAACTAG AACTGTACCT GAGACATAAT 19260  
AAACACTTGA TATGTTTGTA ATTTTAAAT AAGTTAATGA ACGGAATGGC TAGAAAAAGT 19320  
GAGAAGAAAC TCTGGCTTAC TGTATATCAT ACTGTCATAC TAAAAATATA TACTGAAGAC 19380  
AGAATCACAT TATATCATCA CTTTTCACGC TATAGGCCAT GATCCATTAT GAAAAAGAGG 19440  
ATAGTAAAAA AATCACAGGG CACAATTTT GTTCTGTCA CACACATGTG TACCTGTATA 19500  
TTGGACTGGA ATGTAAACG CATGTTCCAT TGTAAGACGT GGTTTTAAA GAGGCTTGGA 19560  
AAACACTGCA TATGGTCATT TCTTAGTTA GTACAATTA TTATTTTCGT AATAACCTCA 19620  
GCTATAATAT AAGTCTACCA TGAAGCATT TGGGGAGATT AAATGAGATG TGAAGGTAA 19680  
ATGTGTTAGA TAGACTGAAT TCATATCATA GCTTGCTCTG ATACTTTACA AAACATTTAA 19740  
CCTTACCCAC AAGTTTATG TTCCTCACTA AAGTCACCT GAGGACAGTA ATGGGATCTT 19800  
CCTCACAGAG TATTGTGAGG AATACATAAG AGAACGTACG TAAATGCCTG GCACCTAGTA 19860  
TTTATTCAAT AAATCTTAGC AATGATGATG ATAACAACAT GGTACCTGGC ACATAAGAGA 19920  
GTAAAAATT AGTTTCTTCA GTCAAATGTG CTTACATTGA TAGTTGATAC TAACTGGGT 19980  
TAAAAGGTCA TTGCTGGCAT CTCAGAAAGA TAGATTACAG TGAAATAAAA AATGACTACT 20040  
GCTTAAATG AATGAAGACT TATTTACAAA GTCATGTTCA TCTGGTACAA TAATGAAGTC 20100  
GCTCAATTGG GAGAAAATGA CAAATAATAC AAGTGAATAT ACAATCTTAC TTAAGACGAA 20160  
AGAAATAGGA CACCAGGCTA ACTATCAGTC TCCTAAACCA CAACTTTATT TCTGATACAA 20220  
AGAGACAGTG AGACAATCAG GGCTTCCCTC AAATAAATTA CTTAATCTCT CTTCAATTCA 20280  
GTTTTGCATC TGTAATATA AATAACTACA ATTCACAGT ATTTCCATTT AAAAGTTCT 20340  
AGTGCAACAT CAGAAACAAG AACTTAGTAG GTGTTCAAAA AGAAATATAA GTTCTGCTTT 20400  
GTTAGCCAGC AAATAGTTGC CTGTTTCTAG CCCTCACTTC TTTTCTCCTA AATCCCTATA 20460  
TTGCATTTAT TTAACCTAAA GTGCTGGATG TGGCACTACG AGAAAGAAAA AGATATTTGG 20520  
TAATCTTGTT AAAATCATTA GACATCCCAG GCTATCTGGA ATCACCTTGG GCTCACAGTT 20580  
AGACATCAGC TATGGCTTGT TTTATTTAAA AATTCATCCA CTGATGCATG ATAATGGAAT 20640  
TCACAGGAGA GCAATTTACC AAAAAAAGA AATTTATTGA TTTATAATGT GAGATATTAA 20700  
TTTAGCCACA AATATTTATT GAGCATCTCC TACATGCCAG GGAATGGACT ATATATGGCA 20760  
GGAAACAGA TACCAATCAT TTATATCAGG CATTTTTTTC TAATAGAAGG ATATTCGCAG 20820  
GAGACAATGC ATAGCACCAT GCCTTGACG TAACAGACAT TTAATAACTA TTAGTTGAAT 20880  
AAAATTGGAG ACTAGAATGA TACATAAAGA GGCAAGAAAG AGCAAAGATA AGCCTTTCTG 20940

FIG. 6.8

AGAATTTCTA TCATGTTTTG CTCAATAGCT TGTCTTTATC CACTGCTTGT ATTTTCCAT 21000  
GTAGCTAATC CTCATTGGTC GTTAGAATTG AGACACCCTT TCCTTGAAAT CAGGAGCTAT 21060  
AGGAGGCCAT TCTTCCTACT GGGCATTTC TTTCTGGGAC AGGGTCTCAC TCTGTCACCT 21120  
AGGCTGGAGT GCATCATAGC TCACTATAAC CTGGAAGTCC TGGGCTCAAG GAATCCTCTT 21180  
GCCAAAGAGG TGGGATTACA GGCATGAGTC ACCATGCCAG CCTATTGGC ATTTCTACTG 21240  
TAGACAAAGC AGACTTACAG CAGTAGGTCT ACCTGCCTAA TACAAAAAGA AAAAAAGAA 21300  
TTTTAACAAA CAAATGAGGG AATCAGATCC AGAAAGTGAT TCTTATAACT TAGATTACTT 21360  
AGAGTAGATC TATAATCTGC TCTAGATCCA CTGCATACAG TGGGCCCTTC TTATCATATT 21420  
CCATAAATAG CACTTTTCTC AGCCCAGCTT TTGATGATAG CTGAACAGAC TAACAGTTTG 21480  
TCTAACAAAG GCTAGAGAAG GGGATAGCAA ATAATGGCCC ACAGGCTGAA TCCTGCCTGC 21540  
TGCTCATTTT TGCAAAGTTT TATTAGAATA CGGTCATTTC CACTCATTTT CACACTGTCA 21600  
ATGGCTGCTT TTGCGCTACA GCAGCAGAGC TGGGTGGTTG GGGCAGGGGT CACATGGCTA 21660  
ACAAAGACTA AAATACTTAT CATCTGACCT TTACAGAAA GTTTGCTGAT CCTTGGAGTG 21720  
TACAAGTATT CTATATTGTT GATTAAGAAC AGAACCACAA GTATTAGAAG TTAGACCAGC 21780  
AGGTGGTAAA GCTGATCATC TACTAATATA ATGGAAATTG GGGTCCCAA TCAGGACTCT 21840  
TGCTTTGATA GAAGGCCATC TTAACGAGGA GGGAGACACC TGCAGGCAAA GTCAGAATTT 21900  
TCTGCAGGAA AAGTTTTGAG TCCATTTCCC CTTGTGAACA AGTGCTCAGC TATGCATTTT 21960  
ATCTTTAGTA ACCATGCTTC TATACCTGGT TCTCCTTGGC AAAGATTTCT TTCTTCAGTA 22020  
AGTCTCAAGA CTTTCTGGGA AGGTAGGGAG ATATGGGGT AAAAGTGTCC CAGGACTTAC 22080  
TGAAGGAAGT GTTTTATGAT TATCTGATAG AATCACTGTA TCATGGTAGA GAAGGCAAAC 22140  
AGAATATAAT CTGAAAATAG AGGTGAGGGT GAACAAATGG GCACTAAAAG TGAACTCAGC 22200  
ATCAGGAAGG TAGCAAAACA AGACATCAGT CAAAGATATG GGGTGATTCA GACCTAAGGA 22260  
AGATTTAATG TGGGATGTTT CCGTGTGCCA GGAGCTGGAC ACTTAAGCAA GAGGAGATCC 22320  
AGGAATGTTG CTAAAACCAT GGCCTCCATA CTTTATTGGA ATTAGCACAA CTTATCCTTG 22380  
TTTCTTTCAT TTTGCAATCA AAATCTTTAA AAACACATTA TTTAAAAATA CATTATTTTA 22440  
AAAGCTAGAA TGAAAATTAT GATATCATTT AGGTGGTTTA AAAACATCC ACCAGCCGGG 22500  
CGTGGTGGCT CATGCCTGTA ATCCCAGCAC TTTGGGAGTC CGAGGCGGGC AGATCACGAG 22560  
GTCAGGAGAT TGAGACCATC CTGGCTGACA CGGTGAAACC CCGTCTCCAC TAAAAATACA 22620  
AAAAATTAAC CGGGCGTGGT GCGGGTGCC TGTGGTCCCA GCTACTCGGG AGGCTGAGGC 22680  
CGGAGAATGG CATGAACCCG GGAGGTGGAG GTTGCAGTGA GCTGAGATCG TGCCACTGCA 22740  
CTCCAGCCTG GGTGACAGAG CAAGACTCCA TCTAAAAAAA AAAACAAAA ACCATCCACC 22800  
AAAATGGGAA GAAGTGATGA AAAATTACAG TCCAAGAAGA AGGGCCATAG CTGTTTAAAT 22860  
CAATTGGTAT ATTTGTTATC TAATATAACC CCACGTAACG ACAGGTATTT AACAAATGTT 22920  
TCTGCTGAAT TTGACGATTC CATTTCCCTT ACATCCCAT TGAATCCAT CAGCACCCCA 22980  
CATCCAACCC ATCAGTACAT CCTGTGAGCA TTGGCTCCCA AATATAACCT AAATCTAACA 23040  
CATATCCTAC TATCTCTGCT GCTACAACCT TAGTCTGAAA TCTCATAATC TCCCACTTGT 23100  
ACTACTGTAG ATGACTCTGA ATGAGTCTTC TTGCTTCCAT TCCACACAGC ATCCATACTG 23160  
ATCTATTTTT TTTTCAATT TTTGTAGAG ACGGGGTCTT GCCATGTTGC CCAGGCTGGT 23220  
CTTGAACCTC TGGCTTCAAG GGATCCTCCC ACCTCAACCT CCCAAAGTGA TAGGATTTC A 23280  
AGTATGAGCC ACTGTGCCTA ACCCTGACTG ATCTTTCTAA GCATAAATCT AATAATGCCC 23340  
CTTCCTTGAT TAAACCCTTC AATGAATTCA CATTAGCAA ACAACCTGGC CAGGTGTGAT 23400  
GGTTCATGCC TGTAATCTCA GCACTTTGGG AGACCAAGAT GGGAGGATCA CTTGAGGCCA 23460  
GGAGCTCAAC ATCAGCTTAG ACAACATGGT GAACTACAT CTCTACAAAA AATACAAGAA 23520  
TTAGCTGGGC ATGGTGGTGC ACCTATAGTC CCAGCTACTC GGGCGGCTGA GCTGGGAGGA 23580

FIG. 6.9

TCACCTGAGC CCTGGAGGTC AAGGCAGCAG TGAGCTGTGA TTATGCCACT ACACTTCAGC 23640  
CTGGATGAAG TGAGACCTGG TCTCCAAAAA AAAAAAAAAA AAAAAAAGA AGCAGGGCAA 23700  
GGTGGCTCAC ACCTGTAATC CCATCACTTT GGGAGGCCAA GGCAGGCCTC CTGGATCATG 23760  
AGGTCAAGAG ATCGAGACCA TCCTGGCCAA CATGGTGAAG CCCCATCTCT ACTAAAAATA 23820  
CAAAAATTAG CTGGGCATGG TGGCATGCAC CTGTAGTCTC AGGTACTTGG GAGGCTGAGG 23880  
CAGGAGAATT GCTTGAACCC GGGAGGCGAA GGTTCAGTG AGCCAAGATT GCCTGGTGAC 23940  
AGAGCGAGCG AGACTCTGTC TCAAAAAAAAAA AAAAAAAG AAAGAAAGAA AGAAAGAAAG 24000  
AAAGAAGAAA TCCTTAGTCC TGTCTTAAT ACTTGAGAGG CTGAGGGAGG AGGATCACTT 24060  
GAACCTAGGA ATTTGAGGCT CCAGTGAGCT ATGACAGCAC CACGGTGCTC TGGTCTGGAG 24120  
AGAGTGAGAC CTTGTCTCTA AAGAAGAGAA AAGAAAAGAA TGAATGAATG AACAAAAAGA 24180  
AAGAAGGAAA GGAAAAGAAG AGAGAGAGAG AGAGAGGAAG AAAGGAAGGA AGGAAACAAA 24240  
ATAAAATAAA ATAATAATA AATAAACCCA AATCCAATT CTTTACCCTA ATCAACAAGG 24300  
CTCAATAAT CTCATGCCAA CTAAGTCTCT GAACAGCTCC TTCCATTCTA TTGCCAGATT 24360  
ACTCCATCTT TCAGCCACAA GACCTTTTTA TCTTCCTTT ACCAGCCAAA CACAATCCTA 24420  
CCTCAGAAC A TGTCACCTT TCTTTTCTC TGACTTGAAT CTCCTCCACC CATTATATAA 24480  
TCTTAGCTCA AAGAGGCTTT TCTTGACAAC TTAGCGAAAG TATTTATCCC AGTCATTCTC 24540  
TGCTACATTA TTCCAATTTA TTTTCTCCAT AGTACATTTC AGCACATAAA GATTTCCTTA 24600  
GTATGTGCTT GTTGCCTTTC CCCAACCTCC TAAATGTCA GCATTCTTG AGGGCAGAGA 24660  
CTGTTTCATT CCTGTATCAT CAGCACCTAA GACAGTTCCT GGAACATACC AAGTACTTAA 24720  
TAAAAATTTG TTTATTGACT AGCTATGACA CATTTTACTT ATATAATTTT ATTTTCTCAG 24780  
CAAAATGAAC ACTTTGAAAT GTAATTAATT ACTGATTTTT GCAGTATTTT CTAATTATTT 24840  
AAATAAAATA TTTACTATTT TGGTCAACCA GAATTCTTAC ATTGTTTTAG CACCCAGATA 24900  
GCTTCTAAAA ATGCTTACAA TTAACACAAT TTTATCTAGC AATATGTATT TATCACTAGA 24960  
CAGAATGCAC TGAACCTTC TTCATTAATA AAAAGCAATC CAGGCTGGGT GCAGTGGTTC 25020  
ACGCCTGTAA TCCTAGCATA GTGGAAGGCC GAGGAGGGAG GATCACTTGA TACCAGGAAT 25080  
TCGAGACCAG CCTGGCCAAC ATGGCAAAAC CCCATCTCTA TAAAAACAC AAAAAATTAGC 25140  
TGGGTATAAT AGCAGACATC TATAGTCCCA GCTACTCAGG AGGCTGAGAG GTGGGAGGAC 25200  
TGCTTGACCC CAGGAGATTG AGGTTGCAGT GAGCCGTGAT TGTGTCAGT CACTCCAGCC 25260  
TGGGCTACAG AATGATACCT CATCTAAAAA AAAAAAAAAA TTAGCCAGGC ATGGTGGCAT 25320  
GCACCTGTAG TCCAGCTAC TCAGGAGGCT AAGGTGGGAG GGTCACTTGA GCCTGGAAGG 25380  
TAGAGACTGC AGTGAGCCCT GGGTAGCCCG CGCCACTGCA CTCCAGCCCT GAGTGACAGA 25440  
GACCCAGTTT CAAAAAACA CAAAAACAG AAAACAAAAC AAACAAACAA AAAAACCCAA 25500  
TGCATTGCTG AAATGTTAAA TCCATTATAA AGAAAAGTAC AGGGGTGGGC ATGGTGGTTC 25560  
ATGCTTGTA TCCAGCACT TTGGGAGGCC AAGGTGGGCA GATCACTTAA GGTCAGGAAT 25620  
TCAAGAACAG CCTGGCTAAC ACAGTGAAGA ATGCAAAATA CAAAATAAGC CGGGAGTGGT 25680  
GGCGCATGCC TGTAATCCCA GCTACTCGGG AGGCTGAGGG GGGAGAATCG CTTGAACCTG 25740  
GGAGGTGGAG GTTGCACTCA GCCAAGATCG AACTCCAGCC TGGGTAACAG AGACTCCATC 25800  
TCAAAAAAAAAA AAAGTAAAAA GTATATAGTT GATTCTGCAG GGACTTAAAA AAGTATAAAT 25860  
ATCTTTTTTA ACATCACAAA GCTCTGATAT CTGCAGGTTT ATGACTAACT ACTAGCTCAC 25920  
TCCCATGAAT ACACGTATGT AAACAGGCTC TATACAATCT ACAATCCCAG ACTAAGGGGA 25980  
AAAACTGTC CTGTCACTGT GGTCTCCAAC CCTTGGCCCA TTTCTTTCCT CTTGACCACA 26040  
AAACTTCTCA GGAGTTGCTT GTTTCCTCTT GATCCACTTA TCTTTAGCCC ACTCCAATCT 26100  
GGCATCGGTT CTCAGTACTC TCCACTAAAA CTGCTTTTAT GAAGGCCATC AATGACGTTT 26160  
ATGCTGCCAA ATCCAGCAGA CACCTCCTGT TTTCTAATTT TTTTATTGT TATTTTTTAA 26220

FIG. 6.10

GAGACTGGGT CTTGCTCTGT CACCCAGGCT GGAATGCAGT GATGCCATCA TAGCTCACTG 26280  
CAGCCTTAAC CTCCCTGAGT TCAAGAGATC CTCTACCTC AGCTGGGACT ACAGGCATGC 26340  
ACAGCTATGC CTGGCTAATT ACTCAATCTT TAACATAGCT GATAATCCC TCCTTGAAC 26400  
ACTCTCAACT TTTAAGAAAC CCTGTTATTT TCCTCCTACA TTTTAGCCA GTTCTTCTAT 26460  
CAGCTTCTCC TTATCTGACC TCTAAATGTT AAGAACATTA ACAAAGACTG AACCTAGTTT 26520  
TTTTCTCCCC TTAGTGTACT GCTCCTGGGC GATGTCAATC AGTCCCATTG CTTTAGATAC 26580  
TATCTGTTGA AACACTGAAA TCACTGGTTT TTTTGT TTTTTTTTTT TTTTTTTTTT 26640  
TTGAGATGGA GTTTCGCTCT GTTGCCCAGG CTGGAGTGCA GTGGTGCAAT CTCGGCTCAC 26700  
TGCAAGTTCC ACCTCCTGGG CTCAAGCAAT TTTCTGCTC CAGTCTCCCG AGTACTGGGA 26760  
TTACAGGTGT GTGCCACCAT ACCCAGCTAA TTTTCTATT TTAGTAGAGA TGGGGTTTCA 26820  
CCATGTGTCC AGGCTGGTCT TAACTCCTG ACCTCAGGTG ATCTGCCAC CTTGGCCTCC 26880  
CAAAGGTTGG GAAAAGATAT CCCAATCTTT TTCCTATGAT TTCTTAATTG ATCTACTTGA 26940  
CATATCCACT TGGACTTTTA ATAGGCATCT CAACTTAAT GTGTTCAAAA TAAACCTCGT 27000  
GACTTTCCT CCCAACCTG TCCCTACCTC CCTCAATAAC TAATATTATC ATTCTTATAT 27060  
TCATATATTG AATAAATGTT TGTTCCCCCA AGTATTTGTT GCTATAAATT TATGAAGAAT 27120  
TCTTTTCTCA CTAGTTATTA TAATTAAAAT GTAATATTTA TTTTCTTTAA AAACCTTTACT 27180  
TTGTAGGATT ATTATTTTTT AAACAGGGAC CAACAATAAA TAACTTCTCT ACTTGATTAA 27240  
AACTAGGGCT TCCTCTTG TGCTCCCTCAGG ACTATTTCTT TGTAACAAACA ATAGGCTAAA 27300  
TCAGTACTGG TGTCAAAGAA ATCATAATCT CACAACCTTA TAAATACAGC ATGTGGCAAG 27360  
GGATTTTCCC ATCTTATATA GTAATAAAT TTTAGCTGT GCCATGGCTA AAAGTTTACC 27420  
ATCAAAGTTG GAATTTTAAA TTAGAGGTAG TCATCTTTCT TTCTTTTAA AGAAATGGAG 27480  
TCTCACTATG TTGCCCAGGC TGGAGTGCA GGGCTATTTG CAGGCATGAC CACAGCACGC 27540  
TACAGCATCC TGGCCTCAAG CAATTCTCCT GCCTCAGCTT GCCAAGTAGC TGGGACTACA 27600  
GGTCCCTGCC ACCACACCCA GCAGAAATAT TTAGCTTTCT GAATTTCTCA AGTGTGTGTA 27660  
TGAATGAGAC TAGTGGGGTC CTTAACCAAG ATTCACAGGA TTTTGTAGTA TTTATTAAAT 27720  
AACTTGGATT TGTATCTACC AGCATGTTCT TTGAGGTACA GGTATGTCTT TTATATCTCC 27780  
TAATATAGTT CATTACAATG CTAAATACTA AGATGTGATG CTCACACACT ACAGAATAGC 27840  
CAAGCAAATG AACTACTTAT TCTCATAGGG CTATTATAAT TAACAAATTC TTGTATCACC 27900  
CCATCATTAT CAACAACAAC ATGATAGGAT TTCCTTTTAT CTTGAAGAGT CTGGAAAAAG 27960  
GGTAACAGAG AGATATTTCT GAGGAACAAA CTGGTAATGA GGGAGCTACT GTGTCCATTA 28020  
CAATACTCCT TCTAGAAGCT CAATACATAA TGACTAATCT CTGGAAAAAA GCAAGTGTGA 28080  
GAATGGAAGG CTCTTCTTCA AACTATGCAA AATGAATCAA TCAGCAGTGA ACAAATTTAT 28140  
GAGCCAAACA AATTCCTACA AAAATTACCA TCATATGCTG TCATGCATGT CTGCCAGTCT 28200  
ATTTATCATA TTATTTAAGA AACAAACATT TATTGAAGAT TTATCATGTG CTCAGCACTG 28260  
CCAAAGAGGA AATAAAGAGC ATAATATCTA TTCTTAGAAA ATAACATTAA CACAAATAGA 28320  
AAACAAGAAA CCATAATGTT AAAAATATTA CATAGTAACA CAGAAAGACA ATGTATAATT 28380  
ATACATACGC ACTAAAGCAA AGATAACATA ATTTATAAAT TATGAGGTAC AGAATAGTTA 28440  
GATTCTGAAA ATTAATAAATA TCAGGAAAAA CTTTCATGAAG ATGAGATCTG GGCTGGATCC 28500  
CAAAGGATAG GCAGGTGGAT CATGTAGAAC AGGGGAAAGG AGTTCCTGAT CGGGGATACA 28560  
ATATATGTAA AAACCTGGAG ACAGGACTGA GCGTGAAATG TTAATGGGAC AGTAAAGAAA 28620  
TCTTCCTCTG CAGCGGGGGA AAAACAGAA TAATGGGAAA CTGCATGGTT AAAAGGTTTG 28680  
ATGTTAAGAT AGTGCTTGA CACAAAAGAT CTTAAAGTTG AGTCAAAAGA GTACAATGAA 28740  
AGCATTAGAA ATAGAAGATA AAACACAATT AGGCCGGGTG CAGCGGCTCA TGCCTGTAAT 28800  
CCCAGCACTT TGGGAGGCCA AGGTGGGTAG ATCACTTGAG GTCAAGAGTT TGAGACCAGC 28860

FIG. 6.11

CTGGCCAACA TGGTGAACC CCGTCTCTAC TAAAAATACA GAAATTAGCC GTGAATGATG 28920  
GCTCGTGCCT GTAGTCCCAG CTATTTGGGA GGCTGAGGCA GGAGACTCGC TTGAATCTGG 28980  
GAGGCGGAGG TTGCAGTGAG CCGACATCGC GCCACTGCAC TCCAGCCTGG GTGACAGAGC 29040  
AAGCCTCTGT TTAACAAAAA ACGGTAAAAA TAAATAACAT TTAATATTGT TTTCTGATGA 29100  
TATATATGGC CTCTAATTGT AAAGCTGAAT GCCTAGTTTA CCACTTTTTT TTTTTTTTGG 29160  
AGACGGAGTC TTGCTCTTGT TGCCCAGGCT GGAGGGCAAT GGCACGATCT TGGCTCACCA 29220  
CAACCTCTGT CTCCCAGGTT TAAGCGATTG TCCAGCCTCA GCCTCCCGAG TAGCTGGGAT 29280  
TACAGGCATG TGCCATCATG CTCAGCTAAT TTTGTATTTT TAGTAGAGAT GGGGTTTCTC 29340  
CATGTTGGTC AGGCTGGTCT CAAACTCCCA ACCTCAGGTG ATCCACCCGC CTCAGCCTCC 29400  
CAAAGGGCTG GGATTACAGG CGTGAACCAC CGCGCCCGGC CTATCATTCT TATTTTATGC 29460  
ATTAGGAAAC TAAGGCTCAA CAAGATTAAG GCTGTCTAGG GTCACAAAGA TTGTAAGTGG 29520  
AGGGGCTAGA ATTCAAAATG AGACCTGCTT GACTCCTAAG CCTGTACCAT TTCTACTATA 29580  
TTTAGAGTGA AGTAGATGGG TTGAAGAAAT ATTTAGGAGG TGAAATTTCA AAAGTGTACA 29640  
GTCAGAAGAG AAGACATATA TGGAAACCTA AATTTTCACA CAGTAAAGTG TCAATAATAA 29700  
AGGCATAATG CCAAAATGAC AGAGGCTGTG CATGGTGGCT CATGCCTGTA ATCCCAGCAC 29760  
TCTGGGAGGC TGAGGCAGGA AGATCACTTG AGCCCAGGAG TTTGACACCA ACCTGGCCAA 29820  
CACAGCGAAA CCCCATCTCT ACTAAAAATA CAAAAAATTA GCTGGTAATG GTGGTACACA 29880  
CCTGTAATCC CAGCTACTCA GGAGGCTGAG GCATTAGAGT CACTTGAACC TGGGAGGCAG 29940  
AGGTTGCCAT GAGCCAAGAT TGTGCCACTG CACTCTAGCC TGGGCAACAG AGTGAGACTC 30000  
TGTCTCAAAA AAAAAAAAAG GAAGACTCGA GGGCTAGAAC CCTGAAATTG GGAATGAACA 30060  
GGACTGGCTG AAAATGTTTC TTGCACCTGA TAAAAATCTT GAAGAAGAAT GCTTTAAATA 30120  
GATAAGAAAG GAGAGAGAGA GGTGGGCGAGT GAGAGGAGAC CACCCTAAGT AATCAGAGAT 30180  
TACTTACGTT GGTACTCAG GCTGGTCTCT GAATCTGATT ATAAATGAAA TAGAGATTAC 30240  
TTAAACAAA GGGCTGTAAG GTAGCACTGT CCAGCAGCAC TTTCTATGAT GGAAATCTTC 30300  
TATATCTGCA CTGTCCAATA AGGTGTAGCT GCTAGCACAT GTGGCCACTG AGTACTTAGA 30360  
ATATAGCTAC GACAACCGAG AGGCTGAATT TTAATTTTAA TTTAATGAAT TCAACAAAT 30420  
TTATTTTAA TACAGCACTT TAAATTTTAT TTTTAAATTT TAATCTATTA TTTATTTAGA 30480  
GACTGGGTTA TGAGACTGGC TAATTTTTGT ATTTTGGTA GAGACGGCGT TTCACCATGT 30540  
TGCCCAAGTT AGTCTCAAAC TCCCGGGCTC AAGTGATCCA CCTGCCTTGG CCTCCCCGCA 30600  
AAGTGCTGAG AATACAGGTG TGAGTCACCA CGCCCGGCCT AAACCTAAAT TTAAATAGCC 30660  
ACGTGCGGGT AGTGGCTACC ATACTGCACA TGCAACTGTA AGATGTAGAA GTCAGATGTG 30720  
AGCAAAGAAA TGACAAGCCG TTCAATGCTG TTAGAGAATG AAATTCAAGG TTCCAATGAT 30780  
CTGAACTTGT GTCCCCTCAA ATTCGTATGT TGAAATCTTA ATCCTCAATG CAACAGTATT 30840  
AAGAATTTGG GGCTTTAGGA GGTAATTTGG TTTTGAGGGT GGAGCCCTCA TGAATAGGAT 30900  
GAGCACCTGA GGTAGCCTCT TTGACCCTTC CACCATGTGA GGACACACCA CGAAGGCACC 30960  
ATGTTGGAAG CAGAGAGTGA GCACTCCCAA GCACTGAAT CTGCCACATC TTGATTTTGG 31020  
GCTTCTCAGC CTACAGAACT GTGAGCAATA AATATCTGCT GTTTATAAAT TATCCAGTGT 31080  
AAAGTATTTT GTTATAGCAG CCTGAATAGA CTAAGACAAA GGTGGACTAA GGCAGGATAA 31140  
CAGGTTAGAA AAGGAGGCAG GGCCTTTTTT TTTTTTTTTT TTTTTTTGAG ACAAAGCCTC 31200  
ACTCTACCC AGGCTGGAGT GCAATGGCAT GATCTTGGCT CACTGCAACC TCCACCTCCA 31260  
GGGTTCAAGC AATTCTCCTG TCTCAGCCTC CCAAGTAGCT GGGATTACAG GTGTGCACCA 31320  
TCACACCCAG CTAATCTTTT GTATTTTATG TAGAGACGGG GTTTCATAT GTTGGCCAGG 31380  
CTAGTCTTGA ACTCTTGACC TTAAATGATC CACCCGCCTC GGCCTCCCAA AGTGCTGGGA 31440  
TTACAGGTGT GAACCATCGC GCCTGGCCGA GGCACAGTGT TTTTACAGAG AAGCCTGTTT 31500

FIG. 6.12

AAGGTTTAAT CATATAAAAT GTATGATATC CAGTAAGTTT TGATATAAAA AAGAAACACC 31560  
TGGCGATTTT ATATAATATA TTGTGCTAAG GAATTTTAAG CACTCTACAT TCTGCTCTCT 31620  
AAGCTCTGTA AAGAGCACCA GGGATTTTTT TTTTTTTTTT CTTTTTGAAC AGGGTCTTGC 31680  
TCTGTCAGCC AGGCTGGAGT GCAGTGGCAC AATCTTGGCT CACTGCAACC TCTGCCTCTC 31740  
GGGCTCAGCG ATTCTCCAC CTCAGCCTCC TGAGTGGTTG GGACCACAGG CGCATGCCAC 31800  
TACATCTGGC TAATTTTTTG TAGAGATGGG GTTTTGCCAT GTTGCCCAGG CTGGTCTTTA 31860  
ACTCCTGGGC TCAAGCGATC CTCCCACCTT GGCCTACCAC GCATGCCTGG CCACAACAGG 31920  
GATTTTTAAA TGTAAGACTA CCTAGTCAAC TCTTATTCTA TATTAACAAT ATAGACAAGA 31980  
AATAACCTCT AAGTAATCTC TATTTCAATT ATAATCAGAT TCAGAGGTTT TCTTATGCTT 32040  
TACAATATTG TCCTACTGTG GGTAGCGCAA TAACTAAGGT AATCTGAAAG ACCAGTTATA 32100  
TTATATACTA TAGTTAAATG CATTTCAACT GCATGGGAGA AAGCAACTGT GTTCTTTCTT 32160  
CTCAATTTTA ACAGAAGGAA AATTGTCAAA ATTAGCTTAT TTAGAATGTC CTATCAGAGA 32220  
ATTATTTTGA TTAAATATA TTTTAAATCA ATAAATATT TCTCTTTGGT CAATACTTGT 32280  
CAATATAGAA TAATATCTAG CCACAAAATT AAAAAAAAAA CATTTTCCCC TATATTACAT 32340  
TCATGGATCT TCTTGAATTT CTGTTATCTA GGTGCTTTTA AAAGTCATAT TTCTGATAAT 32400  
ATGAAATCAC AGCTCCTTTT CTTTGGCATA TTAGTTACT GTATTAAGAA AATGTACAAC 32460  
ACATAATTTA GAATGGGTAA TTATTATATT CTCTTTATTC TTATATTGAA AATGACATGA 32520  
AAATTACCAG TCTTCCCAGG TAATATAATT TAAGTTAAAG AACATCTACA TACTACAACC 32580  
AATACCCATT CCCCTATGTT ATGTTTGAA AAACATAGAA GTATCTTTAG TAGTACTCTT 32640  
AGAAATTATC CCAGGTTTCA CATATTGGTA TTTTATTTC AGGTTTAAGT TACAGTATTT 32700  
TGGGCACCCC AAGTTTAATA AACTATTCCC TGCAGAAACC TGACAAGTGA AGTTGTGGCT 32760  
GGGAATATGT TAGTCTTCAG ATAAATGAA TTGTTTAAGA ATTTGCTAAA GATCTCAAAG 32820  
CATCTTTCTT AAATCTAAAG AAAGTCAGGA ACAAAGCCAC AACCAGGACC ATAGCATCAG 32880  
AAGATGGAAG GTTGCTTTGT CTTCAAATTT AAAAAACATT TTCCATTTTA AAATAATTTT 32940  
ACTATTTACC TGTGATACTG TTGAAAATTA TGAAAAACA GATAATTTAA AATTTAGTGC 33000  
TTTTTTTTTA AAAAAAAAAA AAAGCGAATC CCTGGGACAC TTCATATAGT GCAAAACAAC 33060  
AATTCAAGAA TTCAAGCATT GAAAGAAATA ATCTCTTATC CCCCAGTCTC TGAAAGGGAT 33120  
TGCCTTTACT ACTGTTCCCA TCTTTATGTC CATATGTACC TAAGGCTTAT CTCCCCTTA 33180  
CAAGTGAGAA ACTATTCAGT ATGGCTTAGT CATTTTAAAT GCAAGAGAAT AGGTAAAAAT 33240  
GCCAAGCACC AGCCAGAGTT TTTTCTTTGC AGATAGATGT GACTCTTACA GGAGCAGCAG 33300  
GGATTTCCCA CTTTGGGCGG AAAGCAGCAT TTAGGTATTC CCCCTCCAGT GCAGTTACAG 33360  
ACCACCCCCG CGTAGAAGCT GCTCCTGTCC TCTGTGGCAT GTCAGCCTCT GATTATCTTT 33420  
TAATAAACAA TATGGCATAT TAAGTCTCTT TTATGCCCTT CTTTGTATTG CCAGGTACCA 33480  
CCTCCATGTC AGGATAACAA GAATTTGGTA ATGTTTGTG AATAAATTTA GCAGAAGTTG 33540  
AAAGAAAAAT CCTGTTTCTA CAGAAAGATA CCACTGGCTT TTGGGGAGCC CGAGTTCATG 33600  
ATGAAACTAA AGAAAGCCAC AAAAGTTCAC CTCAATGCCA AGACATTTCT TGATTTTTGA 33660  
AAACCCAGTT GTCGAACCAC CCATCTATAG AAAGTTGAAA GACTAAAAAC TATCTTACTC 33720  
TAAACATTTT CTAGGAAGTT GATTCTACAA CACATTTTGG TTTTCCAATT TGGCTTCTAA 33780  
TAATTATTTT AAAGTTTCTG TGGCCTAAAT TTTGTTTAC ATTGATCCTT TGAATGGACT 33840  
ACTGTTTCCA CATTTTAGAA CATTTAAAAA GATATCTACA ACCCGAGTCT AATCATAAAA 33900  
AAAATCAGAC AGATCCAAAA TGTGGAACAT TCCACTAAAA AAGGAGTGGG GAGAGGTCTT 33960  
TATTCTTCCA AAAATATCAA TGCCATAAAA GACAAAGACG GCTATGGAAA TGTTACAGAT 34020  
TGAAGGAGAC TAAAGTTAAA TGCAAGAAAG GAAAAAATGG CATATAGGAC AGTATTGAAT 34080  
TGACTGACAA AACTGGATTA CAATAGTAGA GTATCAATGT TAACTTGCT GAAGTTGCTA 34140

FIG. 6.13



ACTGTATTTT TTAGGAATTA TTCACCTAAG AATTTAGGCA CACAGATATG ATGTATGTAA 34200  
GTTACCCTTA AATGGCTTAG AAAAAAATGT GTGTATATTC ATTTACATAC GTATCTACAC 34260  
ACACGTGTAT TAGCGGAAGA GAGCAAGGCA CACATGTGCA TAAGTGATAA AGCAAATGAG 34320  
ATGAAATCTT TATTTTTAAA TTTAATTTTG TAAGTTTCAG CTTTTTAAAA TTTTAGATTCT 34380  
CGGGGATACA CGTGCAGTTA TTAGTTGGGT ATATTGTGTG AAGCTGAGGT TTGGACCTCT 34440  
AATGTTCTCTG TTGCCACAAC AGTGAACACA GTACCCAGCA CGCAGTTTTT CAGCCCTTGC 34500  
CCCCCTCCCTC CCGCTCTCCC TCCTTGCTTT TGGAGTTCCC AGTGTCTACT GTTCCCCTCT 34560  
TTATGTCCAT GTGTACCCAA GACTTATCTC CCACTTACAA GTGAGAGCAT GCAGTATTTA 34620  
GTTTTCTTGT TCTGCGTTAG TTCCGTTAGG ATAATTGCCT CCAGTTACAT TCATGTCACT 34680  
GCAAAGGATT TGATTTCACT CTTTTTAATG GCTGTGTAGT ATTCCATGTT GTATAGGTAA 34740  
CACATTTTCT TTATCCACTC ATCAATTAAT GGGCACTTAC ATTGATTTCA TGTGTTTGCT 34800  
ATTGTGAACG GTGCTGCAAT GAACATCTGA GCGCAGGTGT CTTTCTGGCA GAATGATTTA 34860  
TTTTCTGTG GGTATATACC CAGTAATGGG ATTGCTAGCT CAGATAAGTA TTTCTATTTT 34920  
TAGTTGCTCT CCACAGGGGT AGAACTAATT TGCATTCCCA CCAACGGCGT GTAAGTGTTT 34980  
CCTTTTCTCC ACGGCCTCGC CAACATACGT TCTTTTCTGA TTTTAAATAG TAGCCATTTT 35040  
GAACTGGTAA GAGATGGTGT CTCATTGTAG TTTGGCTTTG CATCCAAATG AGACAAAATC 35100  
TTAATGACAG GTGAATCTAG GTAAAAGGCA TACAGACGTT CTTTGTGTTG TTTTTTAAAC 35160  
TTACATTTGA AGTTATTTT AAATGAAAAA TAAAAGCAAG CAAAAAAGG TCATTCTTCA 35220  
TCTAGTAAAC TCTTCAAAGA TTACCACCCC CTTCAACAGT TTTTCTGGT TCTAGTGAGT 35280  
CTTCTCCCAT TTGTTTAGAT CTTTGTGAA ATGTAGTCTC AGATAAAAAA TTGTATTTTT 35340  
ATTTCTTTTA CATATTTCAA ACAATCTAAA TTCTTTTAA ATGAAACTCA TAAAAATAC 35400  
TGCATTTGTT TCTAAATAAA ATGGTAGAGG TAATTTGCAC CTTTCCAAAC AGAAGCAATA 35460  
GGAGCAACCC AGATGTTCTA GCCACGATCC AAGTCAACCA CATTCAATCT AAGAAGTAAT 35520  
TGAAGGCTGT AACGACTTCT GTAAGGCCTA CAAAAATGAG TTCAGACACA AGCTCTGCTC 35580  
AGTAAAAATC TAGTGGCAGA TGATATATAC AATGATCTGA GAAAAAGGCA GAATCAACAA 35640  
AGGTGTATT TTTATCTATT GCTGCGTAGC ATATTTCTT AACTTTAGTA GCTTGAAACA 35700  
ATAAACATTT ATTATTTTCA AAAGTTTCTG TGGTCAGAAA TCCAGGAGCA GCTTAAGTGG 35760  
GTGGATCTGG CTCAGCTGTA GACAAGATGT CGGCTGGGAC GGCCATCCTT TGAGGGCTCT 35820  
GAGGGCTTTG AGGGCTGCAC GATCCAATTG CAAGGTGGCT CACTCACATA CTAGGCAAGT 35880  
TACTGCTGGG TGCTGGGAGG AGACCTTAGT TTCTTATCAC ATGGACCTCT CCACAGGGCT 35940  
GCTGGAATGT CCTCATGACC TTCCCATAG TGAGTATTCC AAGACAGGAA AGTGAAGGCC 36000  
ACAATGTCTT TCATGACCTA GCCTCAAAAG TGACATACTG TCATTTACAC AATATTCTAC 36060  
TGGCTGTACA AGTTAATCCT ATTTAGTCTG GGAGGGGACT GCATAAGGGC ATGAGTAACA 36120  
AGAGGCAAGA ATCCTTGGGG GCCATCTTGG AAGCTGGCTA CACAGAAGAG AAAACACCAG 36180  
GGGAGTGCAG AGAAGGTGCA ATTAACTCA ATTCCTGGT ATGCCAATGG TAAGAAATAT 36240  
TAGGTGATCT CTGGGGTGTA ACCTTTTTAA TTAGTTCTT CACTGAATAA TCTGGCCAGT 36300  
AATTGTAATA CAAAATACGG CACTCTGACA ATATTCTCTC CTTTATAAT CAATTACACA 36360  
CCAGAATATA TATAAGAAA GACTTACAAA GTCACAAGTA ATTGTTTGGT ATTATTTTAA 36420  
TAATCACATA CTAGGGCCCT ACAATTAGCA TTCACAAACA TCACTCCATG TTGGCCAGAT 36480  
AAGTCTGTCT TTATAGTGGT TTACCATACG CGCCTTAGCA TGAAGTTACA TGTGGTTTCC 36540  
TTAGCCATCA GATGCTCCAA ATGCAAAAAA TGTCTCACCA CAGTCACAGA ATCATGGAAT 36600  
CCTAAAGTTA CCTGGGGTTT CTGAAAATCT CATGGGAACA ACTCACGAGA ATTAAGGCTT 36660  
AAGAAAGTGA TTTATCAAAG AACAAAACCA GCAAGACTTG AGTTTAGAAC TCGCAGCAGA 36720  
GTTGTGACTA GAACCTGTTG AAATAGGCAA TGTAGAAACC CAGACTAAGG CACATTCTCT 36780

FIG. 6.14

ACAACCTTTAC TATGCAAGTA TGCTTAGATA CTCCTTAGCA AACAGCAGGC CTTGAGTAAA 36840  
TTCTTTCAGA ACTGAATACA CAAAGGATAC AGAACGGAAT AACTAACA TAGTGCATGA 36900  
TGTGCTCATT TCTGTAATAG AAATGAATTA ATTCTGATCC ATCTATAATT TATTATTGCT 36960  
CCATGATTAA CGGAAGGCAT AGGAAAGATG ACTGGAATAG TGTAAGTAGT ACAAACAAGT 37020  
ATTACACTTG ACTGAACCTC ATTACACTGC AATTGCATAT TATATAGTAT GTAGGTGAAC 37080  
AAATACTGGG TTAGTCAGTG GACCTACATT TGAATACTGG TTCTGCTCCT AGACAGCTGT 37140  
ATGATTTGAA TGAATTCTTT ATACTTTCAT AGTTTCTCTG TTCTTCTCTG TAAAACAAAG 37200  
GCTTAGAAGA TATTATGGGT TAGATTATGC CCCTTACAAA AGATGCTGAA GTCCTAACT 37260  
ACAATACCTG TGAATGTGAC TTTATTTGGA AATAGGGTCT TTGCAAGTGA TAAAGAAGAG 37320  
GTCATGGAGT GACCTAATCC AATACGACCA GTGTCCTTAT AAAAAAAGG AAATTTGGAT 37380  
ACAGATACAC ACAAACAAGG AGAATATCAA ATGAACATGA AGGCAGAGAC CGGGGCGGTA 37440  
CATCTACAAG CCAAGGGACA CCAAAGATTT TCAGCAAATC ACCAGAAGTT AGGAAGAGTC 37500  
ATGGGACAGG TTCTCACAGT CCTCAGAAGA AACCCACCAT GTCAATACAT CATTTTGGAC 37560  
TTCTAGTCTT CAGAACCGTA AGAAAATAAA TTTTGTGT TCAAGCTACC CAATTTGTGG 37620  
TACTTTGTTA CAGCAGTCCT AGCAAACCTAA TACAAATGAG CTCTTAACAC TGGTCTAAAA 37680  
TAGGATAATC CTATGAAATG CTACAAATGT TTGGGAAGAT TTCTCATACT CAACTGTTTA 37740  
CAGTATACCA CAAGCCTGTC AGTTGAAGAT ACAAACAGAC CCTCTATAAT CCTCTATACT 37800  
TATATGCAAG GAACAGCACA CTTTTCTGC AAAAGGTCAG ATAGTAAACA TTTTAGGCTT 37860  
TGTGGGCCAA ACAAGGTTTC TGTTACATTT TTTTTTATA ACTCCTTAAA AATGTAAAAA 37920  
TCACCCTCAT CCCAACGGAC TACAGGAACA GACCTCAGGT CACATTTGAC TCATAGCCTG 37980  
ACCCCTGGTG TGTAGGGTTA ACAAGCCTCC TTTCCCTGGG CTCCTTTTTC TTTCAGCATT 38040  
CCAAGCCAAA GGAAACTATC TTTTCAAAT CATTTTCTCT CCTAGGTGGG ACATCTTACA 38100  
CCAGCCCAGG CATGCTTCCG ATAGCCTTAG AGTAGCTGTC CCTTCCTCAG AATTACTGTC 38160  
TAATTGGCTA GAAGTTAGCA ACTTTTACA TTTTCTTTC AATTCCTTTC CATTAAGAAG 38220  
AAGGCATGCA CCGGCAAATT ACTTGTGACT ATCAATGACA TACTCTCAGA AGCACCAGTA 38280  
CCCCTGTGTT GTTTCTAAAC CCATTCTAAT AGACACATAC CCCAAGGTTA TGCTGTTTGT 38340  
CATCTACAA AATGACTTAC ATCTAGAGAT TTAAATAATT AATGTACTTT TCATAACTAC 38400  
CAGGTACAGT AGATCTGATA ATGGCAGAGC TAAGCACATA TACAGAAAGT AGGGCAAGGG 38460  
CCAGAGACTC ATTTTAAAGC AATGTTACAA GATCGTCACT GTTGCTTTTC ATTTTCTAA 38520  
ATGTGGCCAC TGCTGTTTTT TCACTAAAGG AAATGTTTTA TGTAAGTGA ATAACAGTAC 38580  
CTGGCATAAA ATAAGTGCTC AATAAATGTT AAGGCCTTCT CTCCCTCTTC AACTGGCCTC 38640  
CTCATTTTTC ACAAAGTGAA ATAGAAAAAC AACATGGAAG ATAATCCTGT TGCTTAGGAA 38700  
AAATAACTAA AGCTTGCTAG ACAAATACA CCTGAAAATA TAGGAAGTGA GCTATAGCTG 38760  
GCCTATATGC ATGTATGTTG GAACAGGACA AGATAGTGTA GGGTGGGGTG AAGAGGACAG 38820  
AGAAATGGAA GGAAAGGGGC TACAGCCTTG GTGGCAAAT AAAGGATAAG ACGACTCTTT 38880  
TAAAATGGTC TATTTCAAAT GCTGGGTTGT GAACTTAAT TTGATTACTT CATGAGAAAC 38940  
AGCATCTATA ATCCATCCCT GATTTTCTA CAACAAAAAT TTATTATTTA TTTTATGTTT 39000  
GTGTGTAGAT CTTTATATA TATACATGTA CACACGTATA TGTATATATT ATATATGCAT 39060  
ATGCATATAT ATGTGTATAT ACATATATAA TATATTGTGT GTGTATGTGT GTGTATATAT 39120  
AATTTTTTTA AAGGAATGGG GTCTCACTAT GTTGCCCAGG CTGGACTTGA ACTCCTGGGC 39180  
TCAAGCAATC CTCCACCTCA GCCTCCCAAG TAGCAACCAA CAGTTTTAGT TTTGAAAAA 39240  
TAACAAATAT TAAACACCCA TGTGTAAGGG TTGGTACTGG GCCCTGTGTT AGTTTGCATG 39300  
GGCTGTCGTA ACGTAACACT ACAGGCCGGG CACAACGGCT CACGCCTGTA ATCCAGTAC 39360  
TTTATGAGGC CAAGGTGGGC GGATCACCTG AGGTCAGGAG TTTGAGACCA GTCTGACCAA 39420

FIG. 6.15

CATGGAGAAA CCCCGTCTCT ACTAAAAATA CAAAATTAGC CATGTGTGGT GGCTCATGCC 39480  
TGTAATCCCA GCTACTTGGG AGACTGAGGC AGGAGAATCG CTTGAACCTG GGAGGCGGAG 39540  
GTTGTGATGA GCTGAGATCA GGCCATTGTA CTCCAGCCTG GGCAACAAGA GCAAAACTCT 39600  
GTCTCAAAAA CAAAAAACA AAAACAAAAA AACCCTGATA ACACTACAGA CTGGGTAGCT 39660  
GGACCAACAG AAATTTATTT TCTCACAGTT CTGGAGGCTG GAAATCTAAG ATAAAGTTGT 39720  
TGGCTGGTTT GGTTTCTGAG GCCTCTCTCC TTAACCTGCA GATGGCTGCT TTCTTGAAAT 39780  
GTCCTCACAT AGCTGTCCCT CTGTCTGTTT CTGGTGTCTC CCCACGTATC CAAATTCCT 39840  
CTTCTTATAA AGATACTAGT CATATTGGAT TAGGGTCCAC CATAAAGACC TCATTTAAAC 39900  
TTAATCACCT TTTTACGGCC CTGTGTCCAA ATACAGTCAC ATCCGAGTT CCAGGGGATT 39960  
AGGGCTTCAA CCTATGAATT GGGGGTGGGG CACAATTCAG CCCGTAACAG GCCTAGACCT 40020  
TAATTTGTCA ACACTACAGT TAGATTTATA GTATAGTAAC TGCATCTGTG CTCATCTAAA 40080  
TGTACATCCC AAATGAAATA ATATAGCATG ATGATCTGAA TTTATTAAAG GCAATTTTTC 40140  
CTATAGAAAC CCAAATCTAT AAATTATATA CAACTGTGG TAAGTTACTC GATACCTTGC 40200  
CAGGACTCAT CTATGGTGGT AGATAGACCA CAAAGAGTAC CACTGAAAGA TCCCTTTCCT 40260  
AATCACAGTT TCCTCACTGG CTTGCCACAA AACCTAAAT TCTTCTATTC TTTCATTGGC 40320  
AATTTATTTT CCCTGAAAAT GTAAATAATC TCTGGCAGAG CAATCTATTA AGTGATCATC 40380  
AGCCACTAAC ACCTTAGGGT AGAACAGCTC AGATCACAGT CTAAAATAA ATTCCATCAG 40440  
TATGAAATTT TCTTTATTAC TGCTCCGCTA CTGGAATGTT AGATCACTGT CTGCTTTAAT 40500  
AATAATTCTG GTGTAGGTCA TTCAAATTTT GTTTAAGATA ATAAGACAAA TAGCAGGTAT 40560  
AAAAACATTC CGTCATCTAA TAAAGCAACC CGAGAACAGT AAGAAGAACG TGATGAAATT 40620  
AACATTTTTC AGTACCTGCT AGGAATCAAG TATTCTGCTA GATATTTAG AAATCATCTC 40680  
AATTCATCC TAAAAATTAT TCTGTATAAT AGTATAGGTT GAGTATTCCT AATCCAAAAA 40740  
TCTGAAGCTT TTTTTTTCCT GAGACGGAGT TTTGCTCTTG TTGACCAGGC TGGAGTGCAA 40800  
TGGCGCAATC CTGACTCACT GCAACCTCCG CCTCCTGGGT TCAAGTGATT AGGGATACTC 40860  
AACTGGCTAA ATATAATGCA AATATTTCAA AATCTGAAAA AACCCAAATC TGAAACACTT 40920  
CTGGTCCCAA ACATTTTCAGG CAAGGGACAC TCAAGTTGTA TTAATCCCAT TTTACAGAAG 40980  
AAGAAACAGG CTCAGATAAA TGAACATCTC AGAGCTTGTT GATAGCAAAG GAGAGATTGA 41040  
AACTGTCAGG CCTCTGATCC CAAGCCAAGC CATCACTTCC CCTGTGACTT GCATGTATAC 41100  
ATCCAGATGG CCTGAAGTAA CTGAAGATCC ACAAAGAAG TAAAAATAAC CTTAACTAAT 41160  
GACATTCTAC CACTGTGATT TGTTTCTGCC CCACCCTCAC TGATCAATGT ACTTTGTAAT 41220  
CTCCGCCACC CTTAAGAAGG TTCTTTATAA TTTCCCCAC CCTTAAGAAG GTTCTTTGTA 41280  
ATTCTCCCA CCCTTGAGAA TGTAATTTGT GAGATCCACC GCTGCCCGCA AAACATTGCT 41340  
CTTAACCTCA CCACCTATCC CAAAACCTAT AAGAAGTAAT GATAATCCAC CACCCTTTGC 41400  
TGACTCTCTT TTCTGACTCA GCCCGCCTGC ACCCAGGTGA AATAAATAGC CATGTTGCTC 41460  
ACACAAAGCC TGTTTGGTGT CTCTTCACAT GGACACGCAT GAAAGAAACC CTACCTGGTT 41520  
CTGTGTCTTA CCTGTTGGGG GCCTGTGGTC AAATACTAG TACGGAGTTT TAGTGTCTC 41580  
ACTTTAAAAA TGAGGGTTGT GGCCGGGCGC GGTGGCTCAC GCCTGTAATC CCAGCACTTT 41640  
GGGAGGCCGA GCGGGGCGGA TCACGAGGTC AAGAGATCGA GACCATCCCG GCTAAAACGG 41700  
TGAAACCCCG TCTCTACTAA AAATACAAAA AAATTAGCCG GCGTAGTGG CGGGCGCCTG 41760  
TAGTCCCAGC TACTTGGGAG GCTGAGGCAG GAGAATGGCG TGAACCCGGG AGGCGGAGCT 41820  
TGCAGTGAGC CGAGATCCCG CCACTGCACT CCAGCCTGGG CGACAGAGCG AGACTCCGTC 41880  
TCAAAAAAAA AAAAAAAAAA AAAAAAAAAA AAAAAAAAAA AAAAATGAGG GTTGTAAGGT 41940  
AACTACCTAC TTTTATAGC ATTGTAGTGA AGTTGAAATG AATTAATCCA CATATATTAT 42000  
AGTGTGGTAG AATGCAGCAG AACTGATGAT GTATGACTTC TAAGACTAGT CCTTAAGAGA 42060

FIG. 6.16

CCTGCAGTTT TTGCTTTTGC CCTCTTGGAA CACTCCTGTT GCCATGTTAA GAAAACTCT 42120  
GGGGAGACTA TGAAGGAAGA GAGCATACTC GGGGCAGGGG GGTGAACAGG ACGTGCACAT 42180  
GTACGAGCGT ACAAGCCAGG TGACACCACT ACCACAGCCT CAGACATGTC ACCGGGGATA 42240  
CCAGCACCAC AGCCTCAGAC ATGTCACCGG GGACACCAGC ACCACAGCCT CAGACATGTC 42300  
ACCGGGGACA CCAGCACCAC GGCCTCAGAC ATGTCACCCA GGGACACCAG CACCAGCACC 42360  
ACAGCCTCAG ACATGTCATC GGGGACACCA GCCCATGGT CTCAGACATG TCCCTGAGGC 42420  
CCACTTAGAC CCTTCAACCC CAGCCCAGCT GCTAACTGAC TACAGCCACA TGAACAGAAC 42480  
CAGGTGAGAC CAGAGGAAAC TTCCAGTCAC CTACCAGATC ATGACAAATA ATAAACGATG 42540  
TTTTTTAAAC CACAAAGATT TGGAGCAGCA TTTGTTACAC AAAATTAGAC AACTATTACA 42600  
GTTGACTAA AAACATGTTT ATTTACAATA CTAAATTAGA AGTGAAGAA TGGGAGAAAA 42660  
ACTTCATACT TTTAAAGTCA TTTTTCCTC CAAAACTTC CAACTTTGAA AACTGATTT 42720  
TTATAATGCA TAAAAATTAA AATAACCTTA GAATTTATAT GAGTAGCATA GCCAGCTGGC 42780  
TTTATTATCT GTTGTACTCA ACACTTCAAT AATCACTGAT GTTTTAGAAC TCTTCAGATT 42840  
TAGAACTCTT GCCCTTGCTT TAGTCTGGT TAAGCTAAAT AATTGTTCTT CCTCAAGAAC 42900  
AAATGACCTT ACCTCGTTTT GTTTTCCTT TCTGAGAGAA ACACATTAGC AGTCTCCCAT 42960  
CTTGTTTTTC CTTTTCTGT CACCCAGGAC AGAGGGCAGT GGTGTGATCA CAGCTCTGCA 43020  
GCACGACTTC CCCAGTTCA GGTGATCCTC CCACCTCAGC CTCCAAGGA GCTGGGACCA 43080  
CAGGCACATG CCACCACGTC CAGCTTAATT TTGTATTTT TTGGTAGAGA TCAGGTTTTG 43140  
CCTTATTGCC CCAAGCTGAT CTTGAATTCC TGGGCTGAAG CAATCTGCCT GCCCTGGCCT 43200  
CTCCAAGTGT TAGGATTACA GGTATAAGCC ACCGTGCAGC CTTATATTTT GTTTTAAATT 43260  
TTCTCTGTA TTTTCTCTC TGGCAAATTG TTTAGGGAGT TTCTTAGT TATCAGACTA 43320  
AATTTCAAGG CTTTCCTTCC AATTTTGACA TGTAACAGT CCCTCATTTT TGCTTATCTA 43380  
GTGATTATTC CCAAATCTGT GTTTACAGTC TAGCTGTCTC TCCTGAGATT AAGACTTGTT 43440  
TCTCTAACTA CCTGACGGCA GAATCTCCTC TTGGAAGTAT CAAGGAGGCA GTTCAAACT 43500  
GAACTGGGCA TTGGCTCCAC TCCTTCTCCT TCTCTTTACT ATTAATACCC TTTCTCTCCT 43560  
TCTATATGAC CACACTAAGT CTTATTTAGG CATCGTTTCT TCTGGGAGAC CTTTGTAGAA 43620  
TCTCTGAGGT TATGTTAACA TGCTAAGGTT TTCTTGACAT TCTCAGATTG GGTTAGGTGA 43680  
ACTTTTAGCA ACTTATCTTT TACTAAAAA GTCATCCCTC AGTATCTGTG GGGAATTGGT 43740  
TCTAGGACTC CTAAGGATA TCAAAATCTG CATGAGCAGC CCAGGTGAGA CCAGCAGAAG 43800  
CACTTTACAG TCACCTACAG GATCATGACA AATAATAAAT CATGTTTAAG CCACAAAGTC 43860  
CTTTACATAA AATGGTATAG TATTTGCATA TAACCTACAC ATCTTCCTGT ATCCTTTAAA 43920  
TCATCTCTAG TTTATAATAC CTCATACGAT GAAATACTA CGTAAATAGT TGTTATACTG 43980  
TATTGTTTAG GGAATAATGA CAAGGAAAAA AGTCCACGCG TGTTCAGAAT AGATGCTTTT 44040  
TTTTCTCGTC TAATATTATG GATCCACAGT TGGTTGAATC CACAGATGTG GAATCCATGG 44100  
ATACCAAGGA ACGACTGTAT GCATTTTGAC AATTATACTT CTCATCTTAC CATGCATTCA 44160  
ACAAACAGAA CATGTAAAGC GGTGATAATG CTGTGATGAA AAATAAAGCA GGGGAAGAGG 44220  
CTGCATCCAT CTAGTGGAAG CGATGCCCTT TTCAATCTGC ACAAAGAGAA AAAGCTGCTC 44280  
TCCAAGTTGG GGGGTGGGTG GGTGAGGTAT GTAAATTGGT CAGGAAGGGA TCTGTAGGCA 44340  
CTTACAGATT TGACGCTAAT GAGATGGGAA GCCACAGGAA GGTGTGAAG AAAAGACAAG 44400  
ACATGATCTG ATTCATGTTT TGATCTGATA CACTGGTTGC TAGATGGAGA ATAAGCTGCA 44460  
TGGCGGTGAG AGGAAGCAGA AACAATAGGA GGGTAATGCT ATAATCCAGT GGTCCATAAT 44520  
CCAATATCCC CCCAAGGAAC AGTTCGGCAA TGTCTGGTGA CATTTCTGGC TGTCACAAC 44580  
GTTGGGGCGG AGTGCTACTT GCATCTAGCA GGTAGAAGCT AGGGATGCTA CTAACATCC 44640  
TACAATGCAC AAGACAGCCC TTCCCCAAC ATTGCTGGCC CAAAACGTTG ATAGTACCA 44700

FIG. 6.17

GGCTGAGAAA CTCTGTTATA ATCTGTCCTA GAATGTAGCT TGGATTGAGA TGGCAGTGGT 44760  
AAGAGCTGGA GAAGTGCTTA GCTTCCCAAT GTTTTTTGT TTGTTGTTT TTGAGACGGA 44820  
GTCTCGCTCT GTCGCCCCGGG CTGGAGTGCA GTGGCGTGAT CTCGGCTCAC TGCAAGCTCT 44880  
GCCTCCTGGG TTCACGCCAT TCTCCACCT CAGCCTCCCG AGTAGCTGGG ACTACGGGCG 44940  
CGTGCCACCA CACCCAGCTA ATTTTTTGT ATTTTATAGTA CAGACAGGGT TTCACCATGT 45000  
TAGCCAGGAT GGTCTCCATC TCCTGATCCC GTGATCCACC CACCTCGGCC TCCCAAAGTG 45060  
CTGGGATTGC AGGCGTGAGC CACCGCGCCC GGCCTGAATG TTTTAAAGT ACTGGTGACC 45120  
ATATTCGCTG AGGGATTAAA TGTAAGGTAT GAGGGGAAAA TAGGAATCAG ACACCAGGGT 45180  
TACTGCCTG AGCAATGAGA AGAACGACGT TCCTCATACG GAGATGAGGA AGAATGTGGA 45240  
ATAGCAGGTA AATAGCATGT GCTTGCTTTG TTTGGGGCTG TGCAGAAGAG ACTGATGGGA 45300  
CCAACGTGCT CAGTTCTGGA TATATTAAC TTGGAATGCC TATTTGGCAC CAAGTGAATG 45360  
TATCAGGTAG GCAGATGGAT AAATGAGTCT GAAGTTCAGG GGAGAGGCTG GGGTGGCAAT 45420  
ATGAACTTGG GAGTCTCCAC ATCTGAATAG TATTTAAAGC TATACAACAG GATAAGGTGA 45480  
TTTAGGAACT AAACACAAAT TGAGACGAGA TCCGAGCCCA GAGGCACTCC GATGTTTTAA 45540  
AAAGAGGAGG AACCATCAAA AGATACTAAG GAGAAGCCAA GAAGTAGGAG AACTGAGAGT 45600  
CTGAGAGAAT CATTATACTC ATTTGATCGA CTGCAACAAA TGCTGCTTAG AGGTCAAGCA 45660  
AAATGAGGAC TAAGCAAGGA CCACCAGGTC TGGCAACATG GAGGCCAATG CCGACGTGGA 45720  
AATGAGAGTT TTGGTGGGAA GACAGGAATA AAAGTCTCAC AGGTCTGAAT TCAAGAGAGA 45780  
GAACAGCAGA AGAAGGGTAG AGGTGGTAGC CATAACAAT GATACATTCT CTTGAGGCCT 45840  
TTTCTTGCAA AGCTCAGTGA AGAAACATGG TTCCAGAGAG GGATTTTTTT TTCTCTCATT 45900  
TTACATATGC AAACATATAA AAAAGCTGAA AGAATTGTTT GACAACCACC CTTATTCTTA 45960  
CCACAGATTG AACATTTAAT GCCATATGTT TTCCCTGTAT GTACTGTGTA TTGTTTGAGG 46020  
ATAACTCCC CTCTAAATAT ACCTCGGATG TATCTCCTAA AATAAGTCCA TTCTCCTACA 46080  
TAGCCATAGT AACCATGAAC ACACCTAGGA AAATTAAGAA TATATTCTCA AATATATTAT 46140  
ATAGCTGGGT ATATTACAAT TTCCCAATA TGTGATTGTC AAACCAGGAT CAAGTCAAAG 46200  
TCCATGCACA GCATTTGGTT GTCATGTGTC TTTGGTCTCT ATTAATAATG ATGACTGTTT 46260  
GAAAAGACCT GTCCTATAGA ATAAATTGA CTGATTATGT CATGCCATTG AACTTGTTTT 46320  
TCTATTCTAG AAGGATAGTT TTTTAGGGTA GTGAATACAT TTATTACTCT TGGCACAATA 46380  
GTCTAACATT TCCCAATTTT CTTATATCTC TGCCCTTTCA TTTTCAGAAA ATCAATTATT 46440  
CCAAGATTG TTTTTCATTT ATCATCACTT ATTAGCTCTG AAGACTCAAC TGAGCAACTT 46500  
TCAGGGTTTA TATACCCTAT ATTCAGAAAA AACTACTAC CATCTCTCAT TTACCCTAAG 46560  
AATTCATAGG AGAGCATGTC TTAAAGCTGA TCAATAACCA AACCAAACAT TTTATTGATC 46620  
ATATTACATT TGGAAAGCAA AATGAATTTT CTAAATTTT TTCCCTGATT AGCAAAATAG 46680  
TGCCTCCGAA CACTTGAGGG TGAAAGTTGT TGTCAAATAT GCCTACATGA CTGGAAATTA 46740  
TGACATCCAA ATGAGTTCAC TGGGTCTGAT AATAATATGC TCTACATGCT TATGTCTATG 46800  
TAATAAACAG CTTACATCTG GATGAGAAAA TTGATTATAC AAATATTTGG GCTTCTACAA 46860  
CTGGTCACTC ATCTGTAAGT ACTTAAAGCA ACTTAAATG CAAACTGACC TAACAATGCT 46920  
TATGGTTAGA ATTCCAAAGA ATGTTTAGGC ATTGTCAGGT TATGTTAAAA CATCTTCTGC 46980  
CACAATCTTC AAGTGATTTA TCTTTTCTGT TGTGTTGAAT AGCTATAGAA GACAAATGAA 47040  
TTCTGCACTC CTGAATTCAA TGAACATTTT AAGTTTCCTC ACTTACACTG TAAGATTACG 47100  
TAGCATATTT TAAGAAATAA ATTATAATCA TTTTATTTC CTTATTGAAC TTCTTTTAAG 47160  
CTTTGGCATT AGAATTTTAA TCAAAGCACT GCCACTTGCT TACAGTGATG GTTTTTAGGC 47220  
TCTTTGGGCC TATGGACTAT TTCAATGACC TTCACTAGCC ATCTAGTCCA CCTTATCCTA 47280  
ATTATTACCA CTGCAAAAGA AACCTCACT TGAATAAATC AGTAGATGGG CATGAGGCAC 47340

FIG. 6.18

CTCCCAGGAG ACTATAATTA TTAAC TCATA CTAAAATCAA AATTGTAGCT ATTATCACTC 47400  
ATATGGTTTG GCTCTGTGTC TCCACCCAAA TCTCATCTTG AATTGTAATC CCCACGTGTC 47460  
AAAGGAGAAG CCTGGTGCGA AAGGACTGGA TCATGGGGGC GGCCTTCCCC CTTGCTGTTC 47520  
TTGTGAAAGA GTTCTCCGAT GGTTTAAACG CATGGGACTT CCTCCTACTT GCTCGCTCTC 47580  
TTCTGCCACC ATGTAAGATG TGCCTTGCTT CCCCTTTGCC TTCTGCCATG ATTTTAAGTT 47640  
TCCTGAGGCC TCCCAGCCA TGCAGAAATG TGAGTCAATT AAACCTCTTT TCTTTGTAAA 47700  
TTACCCAGTC TCAGGTAGTT CTTTACAGCA GTGTGAAAAT AGACTAATAC AATCACCTTA 47760  
TGGTAAGTCT GTCTATAAAT CACCTGAAC TACACAGACT ATCTAGAAGA ACATGTAACC 47820  
AGAGTAGTTC TTGATCATGC TATATAAATT ACTGATACAG AAATAGAGCT AGACAGGAAG 47880  
GGGCTGGTAG TAGAGAATCA TCCTCTGGAC ATATTCTCAC AGCCTAATCT CTAGCTAGCA 47940  
AATTTTATAA TATATATAAA AATACAATTA TTTCACAAAA TTACCATGAA ACGATTTTAT 48000  
TGGGATATTA GACATTACTG AATTACTTGT TCTGTGAGGT ATACAGTGAA ATTAACATGT 48060  
TATAAAATTG TGGTAGCCGG CCCCCAAGAT GGCCTCCAAT GAATCCTTCA CCTCTTGTA 48120  
TTCATACCTT TGTGTAGGTA GGTCTGTGTA ACCCATAGAA TACAGCACAG TGACAGTAGG 48180  
TCACTTCCGA GGTTAGGTTG TGAAAGACAC TGTGGTTTCT GCCTCTCTCT CAGATCACGT 48240  
GCTCTGGGGG AAAAGCCAGG TGTCATTTTG TGAAGACACT CAAGCAGCCT TTAGATGACT 48300  
GCAACCACAT AAGAGGCTCC GAACTGGAGC CACTCAGCTA AACCCTCCC AGATTCTCTGA 48360  
CCATGTATCA TTTCATACAC AATGTATGAA ATGACAAATG TCTGTTGTTT TAAGCTGTTT 48420  
GGGGAATAAT TTGTTACATA ACAAATATA ACTAATACAA TAATACATAC TGATTTAACT 48480  
GAAGTTGTAA CTTCATAACT TATTTAGGTA CTAAAAATCA CAGCAACCCG ATGCAAAGTA 48540  
CTAAAAAATA AATCCATTAA TACCTATTGA GACTGTTGA GGGCATGAGG AAAGCTCTTT 48600  
CATACTCCAC ATAAACTTTC CTTACCGTAA TATTCATGGC TGACCTCTAC TCTTAACTCC 48660  
TTTCTAGGAT AGGAGGGGCT AACTGATCTG ACAGCAAGTT TGGGAGAAAA AATTCTGAGG 48720  
CTCGGCCAAC TTCCTCTCTT CTTTCCATTT GGGATTTGGC TGAAGTGAAGA GGGTCATTTG 48780  
TTTTGGCCTG CTCTCTTACA CAGTAAATGT AGTGGGACAA GCTCTATTCT TGTTGATAGA 48840  
AAAACCTCGA TTTTAAATCT GCCTAGTTCT TTGCAGCTCG TTGTTGCTCC AAATCTCAGC 48900  
TACCTTTTGA AACAACTTTT TTCAGTAAAC TTAATTTCAA TCTTCATGTG ATTTAACTGG 48960  
ATCCAAACAC AGGCAGATAA AAAAGGTGGG GCATTACTTA TCAACCTCTA AACTAAGTTT 49020  
AATTTTGTGC CCTCATGGAG TTTATAGTAT ATTTGAGGTT TAAACTAAAA CACCTGGTTT 49080  
TAAACAGAAA CTATAAAAAA CACGATTAAT AGGTGAGGCC GGGCGCGGCG GCTCACGCCT 49140  
GTAATCCCAG CACTTGGGGA GGCCAAGGCG GGTGGATCAC GAGGTCAGGA GATCAAGACC 49200  
ATCCTGGCTA ACACGGTGTG AAACCCCGTC TCTACTAAAA ATACAAAAAA TTAGCCCGGC 49260  
GTAGTGGTGG GAGCCTGTAG TCCCAGCTAC TCAGGACGCT GAGGCAGGAG AATGGCGTGA 49320  
ACCCGGAAGG CGGAGCTTGC AGTGAGCCAT TCGGCCACTG CACTCCAGCC TGGGTGACAG 49380  
AGCCAGACTC CGTCTCAAAA AAACAAACAA ACAAAAAACA AATAGGTGAA AGGCCGTGAT 49440  
CATTGGTAAG CGTAAGAAAA TCTGAGGGAG AAAAAAATAT AGATGCCAG GCCCATGCC 49500  
AAACTCATGG AATCATGCAT GAAACCCAAG CAGCTGCAGT TTTAACAAGT TCCCAATATA 49560  
TAGTTGACCC CTGAACAATG CAGGTTTGAA CTGCCTGGGT CCACTTATAA AATGGATTTG 49620  
ATTTTTTCA ATAAAGTTA CACCGAGTGT GCCTGCCTCT CCTCCCTCCC TCCCTACATG 49680  
CTCCTGCTCT TAAGCCTCTG CCATGAGGCT TAAGACAGCA AGAACAACCC GTCCTGTTTA 49740  
TTTCAATAGT TTTGGGGGGT GCAGGTGGTT TTTGGTTACA TGGATAAGTT CTTTAGTGGT 49800  
GATTTCTGAG ATTTTAGTGC AACTGTCACC TGAGCAGTGT AACTGTATC CAACATGTAG 49860  
TCTTTTAACC CCCATCCAAC CTTCTTCCCC AACCCGAATC CCCAAAGTCC ACTGTATGAT 49920  
TCTTATGCCT CTGTGTTTTT ATAGCTTAGC TCCCACTTTT AAGTGAGAAC ATACCATTTT 49980

FIG. 6.19

TGGTTTCCCA TTCCTGAGCT ACTTCACTTA GAATACTGGC CTCCAGCTCC ATCCAAATTG 50040  
CTGCAAAAGA TATTATTTTCG TTCCTTTGTA TGGATGAATA GTATTCCACG ATGTACATAA 50100  
ACATTTTCTT TATCCACTCA GCTCCTCTTC AGTCTACTCA ATGTGAAGGT GACAAGGACG 50160  
AAGATCTTTA TGATGATCCA TTTCCACTTA ATGATTAGTA AATATACTTA CTTTTCTTA 50220  
TGATTTTCTT AGTAACTTTT TTTCTCTAAC TTACTTTATT GTAAGAATAC AGTATATAAC 50280  
ACATATGACA TACAAAATAC GTTAGTCAAC AATATATGCT ATCAGTAAAC TTCCAGTCAT 50340  
CAGTGGGCTA TTAGCAGCTA CGTTTTTTGG GCAGTCAAAA GCATGGGGAA GGAGAGGGTG 50400  
GTCCCTAACC CCTGTGTTGC TCAAGGGTCA ATTGTAATAA TACCCATTTA AGAATCCATG 50460  
GTATATATGG TAAGTGCAAC AACTCTAGAA GAGAGTGCTA GGAGTTGGAA AAGGAAAGAG 50520  
AAAACAGAAT TTAAAGCAAT CTGTAAGGA CATGCAGGGT TTAGATGAGG TGGAAGGGTG 50580  
AGGGAAAACC AACATCTGCT GTGAGGGCAT ATTAAGTCC AGACATTGTT CTATGTCTTA 50640  
CCTCATTTAA GAGAATTTCA TTTACACAT GGAAAACTG AAGCCCAGAG AGGTTAAATA 50700  
ATTTGCCTGA GGCCAAAATT AGTTAAATA CAGAAGTGGG ATTAGTAGAT GTTTTCATTT 50760  
TATCAGTGAA ACTGAGCCTC AGGGAGGTTA AATATTTTGT ATGAAGTAAC AAACTGAGA 50820  
TTAATATATG GCCAAGTTTA AATGAGATCT GTAAATCTAA TGCCTACACT AAAACAAAAA 50880  
AAAAAAGTG GGAAGAAAAG GTCTATATTG CTTAGCAAAA CAGAGGTAGG GAAGCAAAAA 50940  
TAAACTTACA AAATCAGATT AGACCACCAA AAAACAGTCC CCATTTTAAC TTATGTGGTG 51000  
AGAACCATAT ATTAAGACC ACCAGTGGCT TAAAAATCTT TTTAAAAAT GAATCTGTTT 51060  
TCATTATTCA TTAGTTTTTA TCTAATGAAT AATGTATCTT AACTGATACA TTTACTAAAC 51120  
AATTACCAGC TCCAATTAGC ACTCAGTTAC AATTCAATCA TTAACTGAC CCTCAATTTA 51180  
GCTGTCAACC TAGTCAAAAC AGTTAAGTGA TTTTACGGTC ATCCTCAGTT GCAGAAGTAT 51240  
AATGTTTATG GCTGGAGTCA TTTTATTTT AACTAACATT TTTTAAAAAG ATTGCTTTGT 51300  
AACAATGTGT TATGAGTCCT TTGTGGTAAA TACTGCTTTT TTTTGAGAC GCAGTCTCGC 51360  
TTTATTGCCC AGGCTGGAGT GCAGTGGTGC GATCTTGGAT CTGAGGCTCC TGCCTCAGCC 51420  
TCCTGAGTAG CTGGGACTAC AGGCATGCGC CAACGTGCCC AGCTAATTTT TTGTTTTTTT 51480  
AGTAGAGATG GGGTTTCACC ATGCTGGCCA GGCTGGTCTC GAACTCCTGA CCTCGTGATC 51540  
TGCCACCTC GGCCTTCCAA AGTGCTGGGA TTACAGCTAT TTTAAGGACT TTTTAAAAAG 51600  
TGAAGCTAAA CATTTATTCA TCCCTATTCC TCATCTATAG GGACTTGTGC TCTATTTTC 51660  
TTTGAAGACT GAAGTAAAAA TTCACCTTTG TGAGGGTCTT CCTATAATTA AAATTAATCA 51720  
TTTTTCTC CATAGCTTCT ACAAACATT GCCTGTACAA CTCTATTTAG CACTTATTTT 51780  
ATCCCGCTT GTATGAAAAC TATTTGTTTA CAAACGTTTC TACTTCTCT TAGGAATAAG 51840  
GACTATGCAT TATCACTGT TGTATTCTCC CTGCATTTAT GGCAGTCCTT TGCACATTAA 51900  
ATACAAGCTT TTTGGCTCTG TGCATCTCTT CATCTGGCTG TTCATCTGTA CCCTTTAAAA 51960  
CATCCTTTAT TAAAAAACA GTAAATGTAA AAAAAAAAAA AAGCCATTGA TGAAAAAGTT 52020  
AATAGCTTTC TCAATAAGAA AAGAGTATCA ATTATGCATA CGTCTGAAC ACAAACATG 52080  
AATGAAATAG GCTATTTAAT ACATTCTGTT TTTAAAGTAG GTTTGGTCAG CCATGTAAAT 52140  
TGAAAAATTG GAGCCACCAA GATAACTCAT CAACAAATAT GCACTATGTA CTAGGCACTA 52200  
TATAGATGAT GGTGAACCAA ACAGATGTAA TCCTTGCTCT TACAGATCTC ACAACCTACT 52260  
ATGGGGCCAA AAATATATGT GTATGTGTGT GTGTTATACA TATATACACA CACATACATG 52320  
TATATATACA TATACACATA CACATATATA CATACGCACA CATACACATA TATACACACA 52380  
CATACATATG CTATGAGGAA AACAAACAGG TGGTGAGAAA GAATTAGAGT AGGGGTAGAG 52440  
GACAGAGGGC TCCTCAAATA GGGTGGACAG CTTGACACAA GACACTCGAG CTAAGACTCC 52500  
AAGGATGAGA AGACAGTTAT GTAAAGAAAA GGGGACTAGC ATTGTCAGCA GGTAAGCTAAG 52560  
GCCTTAAAGC AGACAGTCAT GTGCTGCAAT GCCAGCTTCA AGCGAATACA GTTACTAAAG 52620

FIG. 6.20

CATATCTAAC CTTCTATGTG AATGTAGTTA CTAAAGCATA TCCTCCAAC TCCATTTTT 52680  
CTTTTGCTAT TGTTTCTACC ACTTCTCCTT TTCTGTTGAC AATTATTTTA AATTTCTGG 52740  
CTAAATTA AAA TGATGGCATG AACTCTGGGG AAAGTAAGAC TACCTATGTC CAAATAATCC 52800  
TAAATTCCTT CTAGTCCTTA TGA CTGATCA ATTCACCCTG AAGTGACAAC TATGTCCCAA 52860  
TTAGGAAAGA GTGTTTCTT ATCTGCACCT AATTTTTTGA TTTGGAGGCT TCCTGATTGC 52920  
TAATCAACAT GTTGTGTGAT TACTTCAACA AGTACTTATA GAACGTTATT TTGTCACTGG 52980  
AAAAACGTTT TGCTGCTTTC TGAACCTTAG GTTGCTCTAG AGTCTAGGAA GAGTGACTGT 53040  
ACCTAAAGCA GTTCCTAATT ACTGGACATT CTCAGATCTG CTAGAGCTAC ATGTCCAATT 53100  
ACGAGAATAT ACTGGAAAAA GCCCTGGATT AGAAATGAGA GGATGTAGGT TTAGTAGCCA 53160  
GGTCAGCCAC CTTGTTAATG CAAATTTGAG TAAATTGTTA CTTCTTTTAG GCCTTGTTTT 53220  
TGCTGTTTTG TTTTCTGAC AGTATGGTCT CTGTGGTCCA GGCTGGAGTG CAGAGGCACA 53280  
ATATCAGGTC CCTGCAGTCT CTACCTCCCA GGATCAAGCC ATTTTCATGC CTCATCCTCC 53340  
TGAGTAGCTG GGATTACAGG CATGTGCCAC CACACCCTCG AACTCCTGAC CTCAAGTGAT 53400  
CTGCTTGCCT CAGCCTCCCA AAGTGCTGGG ATTAGAGGTG TGAGCCACTG TGCCTAGCCT 53460  
TACACATTGT TTTCTTACTG GTAAAGTGGG AATATCTAGA AGTTGCATGC TACATAAATT 53520  
CAACCATATA TTATTGGCAA AAAATTTTAA AGAAAAACAT CAGCTTAAGA GTACTAATTG 53580  
AGTACATGCC TTGGAATGAG CATGAGCTGG AAAGAACAAA CCTGTTGTTA CATCACTCAT 53640  
TGCTGTTTTT ATATGCTGCT CATTGTAAAT CTTGCTCAGT GGCATGATTT TAGTGTTTAA 53700  
AGATTTATTT GTTTGTTTGT TTAGGACAAA GTCTCTACAC ATAATCTACT TGCTTCATAT 53760  
ATACATACTT ATGCATATTA TGTATGTACA TACATGCTCT CAGGGCTCAC ATGAAAAAAC 53820  
AGCCATTGAG GTGATGTGAT TTATCTCATA TGCTTACTTT AGAGTCAACA GGGTGTTGAC 53880  
TCCACTATAC AATACTGGCA TGGAGAACAC ATAAGTCAAA GTAGACAGGA CCCAGCCGTA 53940  
CCATTGGCTA GGGCACAAT ATATTCACAT ATGTGGAGAA TGATGTACGT AGAAAGGTCT 54000  
TCATTGCACA ATGCTCTTTA ATAAAGATCT GGAAAAAAA AACACCTAAA TGTTCAAAAG 54060  
GATAGGGTAG ATGAAATAAT GGTACATTAT AAAATGGAAG ATTATGCAGC CATAAAAATA 54120  
AGGAAATACC TTAAATAATA ACAGAACAAC TTTTAAGGTA AGTGAACAAA TAAGGTACAT 54180  
AATCACTATG CATAGTATGT ACCATTTACA TAGAAAAAGG GAAGAAAAAT AAAATATATA 54240  
TAGTAATTTA TTTGTTCTTA CATGTGTAAT ATTTTCTGA AAAATATACC AGAACTGGT 54300  
AGCACTGGTT GCTTCCTAGG CAGAAAATGA CTGAGTATCC TTTTGTACCT TTTGAATTTT 54360  
GAACCACGTG AATGAATGTG TTACCTATGA ACAAATGAC AAGTTTAGAT CAGCAAGACA 54420  
GCAGTTTGAG ATGAAATGGG ATTACACCCT TAGTAGGAAA AACTTTTTTA AGCAGGTGGT 54480  
ACTTCTAAGA GCAAATACCT GCACATGGAA TGTTGAAACT ATAAGGAACT CTCCTTAAGA 54540  
GATCCATCTA TTCCAACTT CTCATTTTAT AGATCTGTAA ACTGAGACCT TAAAAATTCA 54600  
GTGACTTGCA TAAGGTCACA CAGCAGAAGA GATGGGATTA GATGCTAGAT ATTTCAATAT 54660  
CAAGTTTGA CTATTAAAA TTCAGTGA CTGTGTAAGGT CACACAGCAG AAGAGATGGG 54720  
ATTAGATGTC AGATATTCCA GTATCAACTT TAGACTATTA TCACACCATC TTCTCATTTT 54780  
CTGGGGGCAA AACAGAACCA AGTAAGTTTG GGCTACATTA CGAGTTGTCA TGTTTTTGT 54840  
TTTGTTTTTT TGAGATGGAG TCTTGCTCTG TCGCTCAGGC TGGAGTGCAG TGGTGTAAATC 54900  
TCAGCTCATT GCAATCTCTG ACCCCCGGGG TTCAAGCAAT TCTCCCTGCC TTAGCCTCCC 54960  
GAGTAGCTGG GTTTACAGGC GCCTCCACC GCGCCCGGTT AATTTTTGTA TTTTTTTTTT 55020  
TTTTTTTTTAG TAGAGACGGG GTTTCACCAT CTTGGCCAGG CTGGTCTTGA ACTCCTGACC 55080  
TCGTGATCCA CCCACCTCAG CCTCCCAAAG TGCTGGGATT ACAGGTGTGA GCCACCACGC 55140  
CCGGCCGAGT TGTCATGTTT TATCTAAATT TTAGAGTCTA ATGTATAAAT TAACCTTAAG 55200  
CCCTGAAACT ACTAATTTCT TGTTTGGATC ACTATACGGC TACACTTAAA AATATGCTGT 55260

FIG. 6.21



GCATACCTCT ATCATTGCAT GTATACAATA TGATAGATGC ATGATATGAC AGACACACAA 55320  
TATGATACAC GTATTTTTTT CTATCCTAAC ACATCTGAAT TTAAGTAAAT AACTAAAATG 55380  
TCTTAAGTTA CTTTTTTAAA TATACACATG CATAGCACAA GCGTGTGACC AAAAATATGA 55440  
ATACAGGTTT ACAATTCCTT AACTAAAACC CAAGGGTTGG ATGTGTTTTA GAAATAAGAA 55500  
TTTCATACAA TTTTAAAGTG TTACAGGGTA TATAAACCAT TATATAACAC ATACCAGGGG 55560  
CCAAGGGCAG CACCCCATAA TCAAACATAT TAATATAGTT TCAGCAAAAC ACATGGGATA 55620  
AAGACTATAT ACAGCTTCTC AATAGTTCAG GTCATATTTT GCTACCAAAT GAATTTTGT 55680  
GCCAAGCTTA AGAAGTTTTT GGTTTTCACC GCTTCTGAA TGTTAGATTG AGATGTGGGA 55740  
TTACAGACTG TACTCATAGA GTGCTTCTAG AAAGCAGTCA GTCACCTCAA CTCTCATTTT 55800  
TTTTTTATGA GACTAAAAAA GAAATCATAG CAAGTAGCTT TTATATCCCA GGTTTGGGCC 55860  
AAAGACTTGT ATTGTGGTTA AGGAATCTAA CTTAGTAGAA GGTGCACGAG CTGACATCGT 55920  
GAGTGGCTAA AATGAGAGAA AAAAAGAGAA AATCCTAATC ATACAGAAGC ACTGAACTAC 55980  
TGCAGCTGTT CGTTAGTTAT TAATTTAATA AAAGCTTCCT CCCTTTAAAT CATGTGAGTT 56040  
TATAACTGGA AATAGGTCAA TAAATTTCT GTCCACACT GCTGACAAGC GATGGACGCA 56100  
ATTAGCTTTA ATCCCACTGG AAGGTACTGC ACTCTCTCTG GGACCAGGAT ATGTAGAAAA 56160  
AAGCATTTCA AATATATAGG AATAACCAGA AATGTATACA GTATTCTCAA CTTGGGACCG 56220  
TTACTCTATA ATATAAACGA AAGGGGTTTT CTAGTCAATC TCTGCTGATC TCTGTACCA 56280  
AAGTTCTTCC CTTTATAAGT CTTGTACTAC CTTTACAAG AGGAAAAAGC TCTAGAGCGA 56340  
AAACACAGAA CACACTAAAA TCCCTTCCTT TCTCTTACA ACTCAAGCCC CGCCTCCATT 56400  
TTGTTTCTGT TACTAATTTT TCTTCTGAAA AAATACCAA TTTACACTGA AAGACTAAAA 56460  
TTCAACTTTG CAGACAACGT TTTAAAAAAT ACAATTCAGT TTGGTGATGT TGTTTTGCAG 56520  
TCTTACAATT TTAGCTACAT TTTAACTGAA CCAATTGTTT TGTTCAATTT ATGAGTTAAT 56580  
ACTCAGCAAG TTTGTTTTTT ACAAAATAGT TATTCCATTC TAAAAATGGA AGTAGCAGTG 56640  
GTGAACAAGA AAACAACCCT CTGAGTTTTG TCTATTTTCA GAGGAAGTAC TACTTTCTCC 56700  
AATTTTAATC ACAATTCATA AAAAAGAAAA ACCTAACTAG CTAGATCTTA AATATACAAA 56760  
TACATTAACA ATCTAGTAAA GCAACAGAAA AAGGTAAACA AACTAACCAG CCTATTTTTG 56820  
TCTGGAGAAA CCCCAACAAA CTGCTGGATT CCTTGGCCAT TTGCATTGAG AAGTACCAA 56880  
AACTAAAATC CTTTTTACTA AATAATTTCT TCTACACGAG ACTTGTTTCC TCCACACCAC 56940  
CCTATCCAAA TTGTCAGCAT TATTCCAGAA TATAATCATT TAGTTTGAGA CCACTAAAAA 57000  
ACCCCGCAGT CAAAATACC AATTGTGGTT TTTCTGTAAA GAAATGGTCA GAACTACAA 57060  
ATTGTTATCC TAGGACACAG AACCAATCGA CAAAAGGAC TTCTGGAATA TGCTGCCCCC 57120  
AAGATTTAGA ATGCACAGGC AGAAATAGCA TACGCGGTCA CGATGTCCCT TAAGCCACAT 57180  
GACCTTCCTA CGAAAGCAAA GGCTTAAACT TATCAAATGA GAACTCCCCC TTTCTCTGAA 57240  
GTTAAAACAA GGCAGGGCAG CTGGAATTAG AGCAGCAGGG ACAGATCGGC TGTTGACTAG 57300  
TCAGAACGGG TCGTGGAATG CAAAGTCCCT GCGCTTTCGC TGCTCCCTT ACCGTGAGAA 57360  
GATCTGGGAG GGAGGAAAGG AGGAGAAACA CCCAGAATC CTGGTAGAAA AGCCCTGGC 57420  
CTCGAAGATG GGCTCTAGGG AGACAGGGAG GGGCAGCTCC GTGTGTGATG ACCCTTTGTG 57480  
AACATGCACT CTGTGGCAGC TTCAGCTCCA CCGAGGCTTT GGGAGAGCGG ACTACGGATG 57540  
CCCGGCGCGG CCCAGCTGTG AAGGCCGCGC CGGCGGAGAG GGTCCATGGC ACCCCGCGG 57600  
GCTTCGGAAG CCCTTCCCTC TCCCACCTCC GCGGGTCACC CCAGGAACCA GCGGCTCCCG 57660  
ACCACGCTCG CGCGGACCAC GGAACAGCGA CGCGCAAGCA GGTCTCTTC GTCAGCGTAA 57720  
TCCCTCCGCA GAAAGCCGCG CACTAGTTTT AATCACGCCC CACCCCTGG CCGCTGGCGC 57780  
CACCTCCGCC ACTCGGGCGC TTTCCAGCAG CTTCCAGAAA CGTCGCCTCC CCAAACCCAG 57840  
CCTCTCACAC ATGGCGGGCT CAGCAGCCAC CGGCCCGCC CCTCTCGTC GCCGCAGTCG 57900

FIG. 6.22

CAACTGCGTC TGC GGCCACA GGGCGGACAG CCACGCCTCT GCGGAGGGCG ACCGGAAGTG 57960  
CTCAGCTCTT CACCTTCCCC GCCACGCCAC CGTCCTTTCA GGCCAGCGT GCAGCAGGAA 58020  
GGAGGACTCT TTTGCCGCGG ACTCAAGCCG GAAGCCGCCT TCCTAGTGGA GACGCGAGTG 58080  
GGGAGGAGC AGTCCGAGGG GAACGTGGGT TGAACGTTGC AACTAGGGTG GAGATCAAGC 58140  
TGGAACAGGA GTTCCGATCG ACCCGGTACC AAGAAGGGGA GTGCCCGCGG CAGGTAAGGG 58200  
AGAAGAGGGA GGGGTTTCTT TCCGCTCTCG AAATTGGGAA AAGAGACAGA GCTGGGATGA 58260  
CCTATGGGGT AGTCGGCGCG CTGAAAGGAT GGGCTGGGCT GGGACGGGGT TCAAGTGGGA 58320  
AAGGTTGATG ATTAAGGTAT AGAGTTGGAC TTACAGATCC GTTTGGGCGC AGAGAGGTGA 58380  
ACGCTGAAGA GAAACCAGAG TTTGTTTTCG TTTTCCAAGG AGCGTGGAGA TGGGCAGGGT 58440  
TAACGGACCC TCGCCTCTCT TCGGCTTCTT AGTTTGGGTG TTGAAACTCA CCTCCTTTGG 58500  
TCCTGTTCTG CTCTGATTCA AGACAGTTGG GTTTGGTACC TGACAGGGCT GGGTGCAGAA 58560  
AGCTGACCCT GTTCCTCGGC TTCCAGGTCG GTTGTTGGCCT CGCTTTTGAC AGTTCACGTG 58620  
CCGAGCCTAC TCGCTCTCGG AGGGCGAGCT CAAATGGGTG GGTTAAGGC CCCCTCTTCG 58680  
AACAGCTGTT TCCCTGGGTT TCTCCATTTT GCACACAGGA GTGTGAATTA AGTTTAATTG 58740  
AATACTTTT GCGATTCCCA GGGCCACCTT GACACGTTCA TTGTGCTATC TAACTGGGTT 58800  
CATGCTGGGC TAATAATTCA CATTAAAGGT TCTGGAGTAT AAGTGGTTCA CAGAAGTATG 58860  
AAAAGGGGAT GTTAGAAGAA AGATGCTGGG GGTGAAGTAG AGTTGAGGAA GACAGAACTG 58920  
GAAAGCTAGG TTGGTTTCAC AGTACAATGA GCTTTAGGTC ATAATACTAC CTTTAGGTTA 58980  
TATTGGGCTG TTTGGACGGA GTTTGCTGTA ATCAGGCTAG AGTAAATAGA GAATTTTAAA 59040  
CTAAGCATTG ACAGGCTCAG ACTTGTAGAG GCATCATTTT GACAGTGATA TGAAGGGAA 59100  
AGAGGTAGAG ATTTGAGACC TTTCCAAAGA ACTGTCCACA GAATTTGGTG ACTTACTGTG 59160  
CGAAGAGGGA AATAAAGAAT AGGGAACAAC TCAAGACTTT CTAGTCTGTG TGTTTGAAG 59220  
GATGGAGACG CCCACATTTA AGTGAGATAT GGAAGGAGG AGCAGATTGT TTTGAAGGG 59280  
AGGAAGAGCA GTTACTTAGG GTCAAATTA GTTGTAATAT CCCCCCGGG ATTTTGTATG 59340  
TAAGTCAAAG TGAATTGTAT TTGGAAGAAG AACTGGGGAG CCCACCTCTG GTATTTTTTT 59400  
TATGTCCCTC ATATGGACAA ATAAACCTCT GGTATTAAAT GAATTTTCTT TTGGGGGATT 59460  
CTATATATTC GGGATTTCAA CCACCAACCT ATCTGGTTTT TCCCGCTGAA ATGTTGGGTG 59520  
ATGGAATCAG GAGAGCAGAT TTGGAGACTC TTTATATTTT ATAATTGAGA GAGACAAAGA 59580  
GAAAACCGTT TGATTTGAAA AAGTTTTCTA GGTTCCCTCA GGTAGATGGA AATTTTCATC 59640  
AAAAACAGTT TATTCAAGGT ACATAGCCTA CTAGTTTCCC ATTTGAGAGT ACCGCAGAAT 59700  
GATACGACGT GTACTGCTTC TCTACGCAGA ATGAAGTATA AAATTAGCAC CAAATAGTAA 59760  
CTTTAATTTG TCAGGTGCTA AACTTTTTAC ATGCTTTATC TCATTTAATT CTTAGAAGAA 59820  
ACTAATTTTA CAAGTAAGTG TCTGGACCAA CATCTGCAGG TACAAAGCCT GAAAAGCGTA 59880  
AGTTTGACTC CTACATAGTT CTCTTTTGTA AGTAGATTAT AAATAGAACC AGCCAAAGGT 59940  
AATAAGTTGT CTGTGCCTAA AAAGAAAGAA AAAAGTTAGC ATCAGTAGTT CTCACCAGAA 60000  
GGGGTGATTT TGCTTACCAG GGGACATTTG GCAAGTCAGG AACTTTTTGG CTGTTGGATC 60060  
TAGAGGGTAA AGGTCAAGTA CGCTGCTAAA CATCGTCAGT GCATAGAACA GCCTTCACAA 60120  
ACAATTATTT GGTCAAAGAT ATTTGTAGTG CTGCAGTTGA GAAATTTCTG TCTTATGGTT 60180  
ATTTCTTCAG GAATAGGAAA TTAAGATTCG CCGATACTTT CTTTAAAAAG CAGTTTTATT 60240  
TTTGAAATTA TTCCTTGGCT TGAAAGGTTT GTGAAGTTTA TATAGCCGAA CCAGAATAGC 60300  
GTAATTAGAT TTTAAAGTGA ATTGTGAGCC ATCGATTCCC AGGAGATGGG TGTCATAGAA 60360  
TCATGGATTC TTGGATTTGG GAAAGACTTA TGCCTAGAAT TATTTTACAA CATTTCTGCT 60420  
AAGTGGTAAT TCTCCTCTGC CCTAAAGGTC TCCTGTATTT GATTTTCCTA TCATTGTGAA 60480  
CCCACAATTA AAATGCTCTT AATTATTTTT TGCTTACACT GAGCTCCGGT CTCTTGAAT 60540

FIG. 6.23

TTTACTCTG TTAAATGTGG TTCTGCACCA TAGGACTGCA CTCAAAACAA GCTTGCCACA 60600  
TATGTAATTT GTACTAGGAC AGTGTTTATA TTTTGTTC AATAACAAAA TAAGTTAAAT 60660  
GTGGTGTAAT TTAGATCATT TACAAATAAT AATTTGTTAG CAGCTTTTAA TAAGTAGTAT 60720  
TTTTCCCAAC TGGTGAAGTA TTAATGTTGG TAGTTGAAAA CAATAGGAAT GTATGGAATA 60780  
TATGGTTCAC TGGTCTTTT GTTCCTGTCA AATAGTGGCA CAATGGATCT GGGGTTTTTC 60840  
TCAGTATAAT GCTGGCATAT TTGTTTCAAA TTGTACATAG ACTCTAAAAA GTTAGGCTTT 60900  
CAAATTCTGG TCAATATAGT TTGCTTTAAA TAGTAGCTGC CTCTACTACA AGTTTTATTT 60960  
AATTTGTTGA CAAATGAGTC TGCTATGAAA ACCGGTCTCTG TTGCCAGTCA CTACCCTCTG 61020  
TTCACAAATT TGCTGGGTTT ATAAATATAG GTATCATTTC CACTTCAAGA TTATAATTTT 61080  
AGAATATGTT TATTCTAGGA CATATAGCCC TCAAAATCTG CTTACTATAT ACGTCTTATA 61140  
AAATAGCATG GTTCTTTTT ATAGTAAATA GAATTTTTAT TTAATTGTCT ATTGACTTTT 61200  
TTTTCCAGG GTTCATTGAA AAAATCCTTA GTGATATTGA CATGTCTCAA GTGACATAAA 61260  
TTAGCCAATG ACTCGGAATG ATGGATTCTC CGAAGATTGG AAATGGTTTG CCAGTGATTG 61320  
GACCAGGGAC TGATATAGGG ATATCTTCAC TCCACATGGT GGGGTATTTG GGAAAAGTTA 61380  
GTGAACCTAT TTTTGCCTG AGTGCAAAGT TTTTTTTTT TCTCTATTTT TGAGACTTAA 61440  
ATTCAATTTT GATGTTACCA GTTAACCTCT AAAAAATTGT GTCTCCACG GAAATCTTAC 61500  
AGTAATGGCG AAAGATTGTT TTAATGTGTT TACCTTCTG TGTTTTATTG ATACATGAAA 61560  
GTGGAAATAA AACATAGACC TTATGATTTA CTGTTCTTTG AAAATATGGT ACATAAATTC 61620  
TCCCGGGTAA TTGATGTTAC TTTTTCCTT GCAAATAAAA TTGATACTAT TCTTAACACA 61680  
TAAAATTTAA TATTTAAAC TATAACATAA TTCTTTTGG AATAATAGCT GTATTTAAAG 61740  
GCTTATATGC ATTTCTTTT TTTGCCATGT TAAAATACC TTGTCAGGAT ACTTGTAATT 61800  
GAAAATTATA ATTTTCTG GTTACCTTTC CATTTAACTT TTAATATTTT GATATATTCT 61860  
AGGAATGTCT ATATTTTAAT TTGCTTTATT TCTCTTTAG AATTTTGATT CAGCTAAAGT 61920  
TCCATCAGAT GAGTATTGCC CTGCTGTAG AGAGAAGGGA AAGTTAAAAG CCTTAAAGAC 61980  
TTACCGAATT AGTTTTCAAG AATCTATCTT TTTGTGTGAG GATCTGCAGG TAAAGTATTA 62040  
ATCTTATATA GTATATATAA GATTTTCTT TTTTCTTTG CTTTTTTATT AATTGTTTAA 62100  
AAAGTTTACT CATTTTTTGT TTTTLAGACT AGATTTTAA TATGTAATCT CAGTTTGTA 62160  
GTCTGTCTGG TATACAATGT TATTTTCCA CCTACCTTTA CTTGGTTGCG TAAAGATGTT 62220  
CGTTTTTATT GCCATTTGAT TTGCGAGAGG AGAAAATACA TTTCAAGGTT TTTTCTTTT 62280  
TTTTAACCT TTTGGAGGTC CTTGTTAGCT ATTAGCATAT AGTAGTACT CTCTCATCTC 62340  
TTTGGTTTAT CTTTGCAACT GATGGGAAAA GTTATGAATT TCTAATGTAC CTGGAAGAGT 62400  
ATTTTGAAA TTGGTTAGTC CAAAACCACT ATATATACTC TGAAGTAAAG AGAGTATAGA 62460  
ATCTTGTAAT TTCTAAAAGA TCCTTTTAGA AGCTCTAAAT CGCTTTTAGA ATTATAGTAA 62520  
TTTGTACCGA CTGGTACGGC TTTTATATAG CAGCTCATT AATTCTGTAA TACTCCACAT 62580  
TTTATTGTAT TTGACAGTTT ATGAGACTGT CTCATACACT TTTAATTCTC AGAAGTTTGC 62640  
AAGATTTGTA TTCCTATTTT ATGAATAAGA AAATAAATTG ATTTGAGAGG GTTTGGGAAC 62700  
ATAAGATCCT GATACAGTGG CAGAGCTGTG GTTGAATAC AGACTTCTAA TTTGAGATCT 62760  
GTTTATTCCA GCAAAAAATT AGCAGTTCAT CAGAATTACC TGGAGTGCTT TTAATAAATT 62820  
TCTGAGTATC ACCCCCAGAT GCTGATTCAA TAGAGTTGGC CCAGAATTCT GTGGTTTTGT 62880  
AACATTTGAG GATGAGTCTG ATCATCATCA GCCAGGTTTG GAAAATACTA GACTAAATCA 62940  
CATGGTTGTT AATAGATACT TATGCTGGGT ATAATTTGAA GTAAAGTAAT CCCAGGCGTG 63000  
TCTACAAATA TAAATTTCTT TATGTTTATA TTCAGTAATT TTTTATGA GTGTCAGTGT 63060  
TTGGCACTGT TGCAGATACA ATGTTAGGAT ACAATAATAA AACAAAAATT TCTTGCCCTT 63120  
AAGGAAGTTA TGTCATAGAG TGGGAAAGAC AGTGAACAAG TATGTGTTTT TCTGTCAGGT 63180

FIG. 6.24

GATAAAAGT GCTGTGGAGA AAAATAAGGC AGTAGGGACT GGAATGCCAA AGTAGGGGGA 63240  
GTTTGCAATT TTAAATAGGA TGGTGAGGGG AACGCTTCAA TGAAAAGTGC AATTCGAGCA 63300  
AAAGCCTGAA AGAGGTGAAG AGCAGTGAGC TTTCTAGGCA GGGGAAGCAA GTTCCAGGAA 63360  
GGCCCTGAGA GAATGGAGGC TGCCTGTCAT GTTTGTGCTA CTGCAATGAA AGCAGCAGAG 63420  
CGATAGAAGG TGGATCAGAA AAATAATGGG GGAGCTGGAC CAAGTAGGGT CTTATAAGCC 63480  
ATTGTAAGCT TTCTGGCTTT TACTATGGGT GAAACCAGGA ACCATGGCAG AGATGTTGGC 63540  
AGAGGAGTGA CATAAGTTGA CTTCAAGTGT AAAAGCATT CTGTGGCTGC ACTGTTGAAA 63600  
ATATATGTAA TGGGCAAGAC CTGAAGCAGG GAGATTAGTT ATAGTATAAT ATGAATTATA 63660  
TTTGGTCCTT GTCTATGGTT TCCGTTACAG AGCTAAAAGT CTTGGAATTT CCTGAATGAT 63720  
AAGAGTGTCC TGTTATTCAG AATGAGCCTG TTTGCTAACA CCGGGGTTCA TACTATTGTG 63780  
GTGACTTAGG ATGGAGCCGT AGATAGCCTC AGATGGGGCA AGTAGCTGGA AAGACCACAT 63840  
GATTAGAGAA TTAACGGGTT AGAACTTTTA GCCCCACGTA CAGGCCTCCA GGAAAGGAGT 63900  
GGAGGGGCTG GAGATCAAGC TGTATAAAAA TATCAAGATT TGGATTTAAT GAGTGGGTTG 63960  
CTGGGGGCTG GTGCCGTGTA GGAGGTGGTA TGCTTAGAGG AAGTGGAAGC TTCATACCTC 64020  
TTCTGTCCCA TACCTTGCCC TACTCATTTT TTCATCTATA CCCTTTATAA TATCCTTTAG 64080  
GATAAACCAA TAAACATAAG TAAGTGTTTG TTTGAGTTCT GCGAGCTGTC CTTGCAAAC 64140  
AGTTATGCCC AAGAAGGGGG AGTGGGAACC TTTGTAGCCA GTCAGTCAGA TGTACTGGTG 64200  
GCCTGGATGT GGGATTGGCA TCTGAAGTGG AGGGAGTCAT GGGACTGAGC CCTCAACCTG 64260  
TAGGATCTGA CATGGTCTCT AGGTAGATAA CATCCAAATG GAATTGGATT ATAGGATACC 64320  
CATTTGGTGT CCTCTGGAGA ATTGCTTGGT GTGGGGAAAA AGCCCCCACA CATCTGGTCA 64380  
CAAAAGTGTG CTGGGAGGAT AGAATATGTG AAAATTGTCA TAATCAAAAT GGAGTCACTT 64440  
GTGTTAAAAA AGAAAAAAAA ATCCTGACTG GCCAGGCACA GTGGCTGACA ACTGTAATCC 64500  
CAACACTTTG GGAGGCTGAG GCAGGAGGAT TGCTTGATCC CAGGAATTGG AGACCAGCCC 64560  
ATGCAACATA GTGTGGCCTT GTCTCTACAA AAAAAAAT TAAATTAGC TGGGCATGGT 64620  
GGTGTGAGTC TGTAGCCCCA GCTACCCGGG AGGGGGACTA CGGGTGACG GCACCATGCC 64680  
CAGGAGGTCC AGGCTGCAGT GAGCTGTGAT TGTGCCACTG CATTCCAGTC AGGATGACAG 64740  
AGTGTGAGAC CCTGTCTCTA TTAAAAGAAA AAAAAAGAC AAATAGATCC AGGAAAGGCT 64800  
ATGAAGAGAG AGCTTTCATG CATAAATACC AAAATATCTC AAAAGACTCT GCAAAAACCA 64860  
CACCTTGCA CAAAGGCCAT CATGAAATAC TTCTGAAATA CACAGAAAAT ACATCATGAA 64920  
ATAAATACAC AGAAAATACT TCTGCAAGGA CATCTGCCCA GCAACTGCCT GGTCCATCTG 64980  
TGGACGGGTG TCATCCTTGT TATTGATCCT TGTAGCCAAG GGTAATTATC TCAAAACAAG 65040  
TATGTGATCC TCCTTATTTT CCTTTAAAAA CCTTTGTCT TCCCTTACCT CCCTGAACAC 65100  
ACACAGTTTA CTATGGCATG TGTATTCCCA TTGGAATACT TTATTCCTGA ATAAATGTCA 65160  
CTTTCTTTT AGAAGCTTCT CTTTCTTTT TATTTAGATT GATAAGTAGA AAGGAAAAA 65220  
AGCTTTTTT CCTTTGGACT AGTTGAAGGC AGTTGCAGTA TTCTGGGGGA GAGGGTGGTG 65280  
GCAGAGGTGT TGAGGCATGG TTGGAGTTTA TTTATACTTT GAAGGTAAAG CCAACAGGAT 65340  
TTGCTGAAAG ATTGGGATAT GGGGTTGGAA AGAGGAATCA AGGATAGTTC CAAGATTTT 65400  
GGCTTGAAAA ATTAGAAGAA TGGAATCGTG AATTACTGAG CTGGGAAGAC TTGGAAGAGC 65460  
AAGGTTTTGG GGAGAAGATC AGGACTGTAA GAATAGAGAA GTCCTTGTCC CCAGGAGTTA 65520  
GGTTTTTGGC TATTAAAGTT AGATGTACTA CATAGATTTT TAGTTGGTTT TTTGTTTTT 65580  
GTTTTTTTT TTTTTTTTT TGAGACGGAG TCTCGCTCTG TCACGAGGCT GGAGTGCAGT 65640  
GGTGCGATCT CGGCTCACCG CAACCTCCGA CTCCCTGGTT CAAGGGATTC TCCTGCCTCA 65700  
GCCTCCTCAG TAGGTGAGAT TACAGGCATG TGCCACCCAG CCCAGCTAAT TTTTGTATTT 65760  
TTAGTAGAGA CGGGGTTTCA CTATGGCCAG GATGGGCTTG ATTTCTGAC CTCAGGTGAT 65820

FIG. 6.25

CCACCCACCT CGGCCTCCCA AAATGCTGGG GTTACAGGTG TGAGCCACCA CGCCCAGCCC 65880  
GGAGTTTTGG TTTTGAAGC ATTCTTTTTC AAGTGATAAA GCAAAAAATA TATAATCAAG 65940  
AATTTAAGT ATATACTTTG GAAATGTAA AAAGGAACAT GAGTAATTTA TTATTATTTT 66000  
TTTAATTTCT AGTCAGCAAT GAGAGCCCAG TGTACTTTAT GAAGTAGATT GGTTTACACC 66060  
AGGAGTGAGC AGACATTTTG TATGATGCAC AAACAAGGAA TGATTTTTTT GTTTTTTAAA 66120  
TGGTTAGGAA AATATCAAAA TAAAAATGC CAGAAAAAT CAAAAGAAGG GCCAGGTGCA 66180  
GTGTTTCACA CCTGTAATCC CAGCACTTTG GGAGGCCAAG GTGGGTGGAT TCTCTTGAGG 66240  
TCAGGAGTTC GAGACCAGCC TGGCCAACAT GGTGAAAACC TGTCTCTACT AAAAATACAA 66300  
AATAGCCGGG TGTGGTGGCA TATGCCTGTA ATCCCAGCTA CTTGGGAGGC TGAGGCAGGA 66360  
GAGTCGCTTG AAGCCAGTGG CAGAAGTGC AGTGAGCCAA GATTTGAGCC ACTGCACTCC 66420  
AGCCTGGGCG ACAGAGGAGA CTCTATCTCA AAATAAATAA ATAAATAAAT AAATAAATAA 66480  
ATAAATCAAA AGAAGAATAC CCTTTCATAA TATGTGAAAA TTAAATGAAA TTCAAATTTT 66540  
AGTGTTTATA AATAAGTTT TACCGGAACA TAGCCATGCT CAATCATTTA TGTATTGTTT 66600  
ATGGCTTCTT TTGCATACAA CAACAGAGTT GGGTAGTTGT GACAGACTAT GTAGCTCATA 66660  
AAATCTAAAT ATTTATTATC TAGCCCTTTA TCAGTAACT TTGCTGATCC CTGTATAAGT 66720  
CCTCTGAATC AAATTATTTT CAAAGAGTTC CGTTATAAAA TTTGGAGTTT ACTCTGCTGT 66780  
AAATTGCAAA GAACCATTTG GAAAACCTCT TTAGTCAGG TATTTACATT AAAATGTTCC 66840  
TTGATTTGTA AACACTAATA TTCAAGACTG GTCCAAAATT ATACCAAATT GAACTCTCA 66900  
AGTGTTTTTA AACAGTAGGA AGTTTAACT TTTTTTTTTT CGTGGAGTAG TCTATCATTC 66960  
AGCGTTTACT TTGGAACATT TAATTAGTCT TTTTAAAAA CCCATGAAAT TTATAATAAA 67020  
AATTTAAAT CATTAATGTT GAGTAATCAA AGAAAACCTT TTTTGTTTTT TCCATTTGTA 67080  
AAATGAGTAC ATTATTATTA TAATTGTCT TTGGCCATAC CTTGTTGATA ATTACTTATA 67140  
CAAGTATAAG AAGACATGGT ATGTTTTCTT TTTTCTATT TCACAAGAAT AAGTACAGGA 67200  
ATTTACTTAA GCTGCTCCAA AACTCAGTGA AAGAGACAGG ATTAGGTTTT TTTGAGCATT 67260  
GGATTTTAAA TGATACTAGA TGGTTGCGCT GGGCTAAAAT ACTAATGCTT TGTGTATATT 67320  
TTTATGACTT TTTTGAAGAC AGCTTAAAAG CTTTATTCTA GTTATAAAAA TGATACATGT 67380  
TCACTGTAAA TAGAAACAAG TCAGGTATAC AGAGATACAA ATATTTAGAA CATGTGAAAA 67440  
GAGGCAACAA AATTTTATAA AAAGAAAAAA GATAAAATC TGAAATCATT AATTTATAAG 67500  
GGAAAAATCA GGGCAAGGAC AAATTATATT ACAGATTGGC CTATGGTGGG AGCACAGATT 67560  
ATATAGAGAA AAGTCAGTGA AGACACTTGC GAAGAGTGTG GGTGGAATC ACTAAGTTTT 67620  
GCAGTCCCGG GGCCTCTTAT GGTATTATAC TGTTTTGTTT TTTTTTTTTT TTTAATATGC 67680  
ATTCCTTTGG AACCAAGGGT TTATTATGTT TTGAATAAAG TAGAGGTGTA AGTAGGATGC 67740  
ATATACCATG ATCTTGACTA CTGAGATTG ACAAAGGGT TTCGTCTCAG GATTTTTTTT 67800  
TCTCTTAAAA AAATTGTAT TAATTTTAA ATTGTAAAAA AATTCATCAA CTTAACCATT 67860  
TTTATGTATA GAGTTCAGGA GTATTAGGTA TATTCATTG TGCAGCAGAT CTCTAGAAT 67920  
TTTTTCATCT TGCAAACTG AACTCTGTA CCCATTAAAC AACCATTCC CATTTTCCTC 67980  
TCCCCAGCT TCTGGCAACC ATTCTAGTTT CTGTTTCTT TCTTTTTTTT TCTTTTGAGA 68040  
TGGAGTCTCT GTCGCCAGG CTGGAGTGA GTGGCATGAT CTCGGCTCGC TGCAACTTCT 68100  
GCCTGCGGGT TCAAGCAGTT CTCCTCCCTC AGCCTCCTGA GTAGCTGGGA CTACAGGGGT 68160  
GCACCACCAT GCCTGGCTAA TTTTTTTTTT TTTTTTTTTT TTTGTATTT TAGTAGAGAC 68220  
GGGGTTTCA CCATGTTGGC CAGGCTGGT TCGAACTCCT GACCTCAGG GTTCTGCCTG 68280  
CCTCAGCCTC CCAAAGTGCT GGGATTACAG GCTTGAGCCA CTGTACCCGG CCTCTAGTTT 68340  
ATGTTTCTAT GAATCAGACT CAGTACCTCA TATAACGGA ATCATACAGT ATTTGCCTTT 68400  
TTTGTGACTG GCTTATTTCA CTTGGCATAA TGGCCTCAAG ATTCATCCAT GTTGTAGCAT 68460

FIG. 6.26

GGATGAATAT ACAGTTAGGA GTTCCTTTTC TTTTAAAGT CTTAATCTCC AGTTTATTTT 68520  
TGTTTATTTA TTTATTTTAT TATACTTTAA GTTCTGGGAT ACATGTGCAG AACGTGCAGG 68580  
CTTGTTACAT AGGTATACAC GTGCCATGGT GTTTTGTTGC ACCTGTCAGC CTGTCATCTA 68640  
CGTTAGGTAT TTCTCCTAAT GCTATCCCTC CCCTAGCCCC CTACCGCCG ACAGGCCCGG 68700  
GTGTGTGATG TTCCCCTCTC TGTGTCCGTG TGTTCTCATT GTTCAGCTCC CACTTACGAG 68760  
TGAGAACATG CGGTGTTTGG TTTTCTGTTT CTGTGTTAGT TTGCTGAGAA TGATGGTTTC 68820  
CAGCTTCATC CATGTCTCTG CAAAGGACAT GAGGAGTTTC TTACTTTTAA GGTGAGTAA 68880  
TATCCACAT TATGTGTATG CCACATTTTC TTTATCCATT CACCTATCTG CAGATGTTTG 68940  
AGTTGCTTTC ACTTTTTGGG AATTGTGAAT AATGCTGCAG TGAATGTGGG TGTGCAGGTA 69000  
CCTTTTCAAG ATTCTGCTTT TGAGTTTTTT TTGGATACGT ACCTTTTTAT GATGCTTTAA 69060  
ATACATATAT GCTATTTTTA AAGGATTCTC AGTTTTCTGA CATATGATAG GACTTAGGAA 69120  
GTAATCTCAA AGCATCATGT TGACAGGTTG TTAGTTGATG GTGACTGCAG CTAGTTGGAA 69180  
AGTCAGAAGA ATCTAGAACT TGTCCATTTA TACTAAAGAA TTTCATAGTA AGTGCAGTAT 69240  
TATGAGTGTA ATGTTCAATT GGTAGAAGAG GCTATCTGAG GGGATTTAGT GCATTTTCAGT 69300  
TATCTGTTGG TGTGAAACGA ATCACCTTGA AACTTAGTCG CTCAAAAATT TTAATGGTGG 69360  
CTGGGCATGG TGGCTCACAT CTGGAACCTC AGCACTTTGG GAGGCCGAGG CAGGCAGATT 69420  
GCTTGAACCC AGGAGTTTGA GAGCAGCCTG GGCAACGTGG TGAAACCTTG TCTCTACAGA 69480  
AAATACCGTG GCAGGCGCCT TTAGCACCAG CTAATTGGGA GGCTAAGGTT GTAGGATCTC 69540  
TTGATCCCAG GAGGCAGAGG TTGCAGTGAG CTGGGATCGT GCCACTATAC TCCAGCCTGG 69600  
ATAACAGAGC CAGACCCTGT CTCAAAAAAA AATTTTAATG GCTCCATTTA TTATTTTACA 69660  
TGATTATGTG AGTTGACTAG GGAATTCTTA CACATCACAC CATGTCAGCT GGGACAGCTG 69720  
AAATGTCCAC ATGGCTGGCA GTTGGTACTA GCTGCTAGCT GGAAGTTGAG TTCAAATAGT 69780  
CAGCCAGGGG TCTCAGTTAT TTTCCATGAG GTTCTCTCCA TGAGGCCAGC TGGGCTCTTC 69840  
ACAGTGTGAT AGCTGGGACT AAGAAGGAGT GTTCAGAAG AAGGGCTTGT CCTCTTGAGC 69900  
CAGTGCTTAT CAGGCCTCTA TGTATATCAT GTGTGCTAAT GTTCCATCAA AGCTAGTCAC 69960  
AGGGCCAAGC CAACTCTGTA CAGTGTAGGG ACTGGCTGCA GGAGGGCATG AATTACCAGG 70020  
AGGTGTAGTT CTCTAGTTCA TAGGGAGGGC CATCAAGATA GTAGTCTACC ATACTTGTGT 70080  
AAAAGAAGGC ATTAATTAAC TATTATTATT ATTATTATTA TTATTTTAGA GACAGGGTCT 70140  
TGCTCTGTTG CCCAGGCTGG AGCAGTAGAG TGGGGCAATC ATAGCTCATT GCAGCCTCCA 70200  
ACTCCTGGGC TTAAGCAATC CTCCCATCTC AGCCTCCCAA GTAGCTGGGA ATACGGGAGT 70260  
GTACTGCCAT GCCACCTGA AAAAGAAGGC ATATTTTAAA AGCAGACCTT TAGTGTAGAG 70320  
GGTTCTTGAA TTTGTTATTT AAAATATTCT GGTAGTTTTT AAACCTAGGA AAGACCCACT 70380  
GATTCTTTTA GTGATATGTT TACATTGTTG TTATTTGGCA TAAATTGTGT TAATGCACAG 70440  
TAAGATTTCA TGAAGTCATT AAAATTCAGC CACTTGGACT CTAAACCCAA TAAAGATGTA 70500  
AAACAGCAGT GCTATGAGAT GCATATTCAG TTTCAAATA TAGGAAACAC AGAAATTACT 70560  
CTGTGCACTT TTAATTTGAA AATACTTTTA AAATGTGTAG TATAATGTAG TGTCTGTCCC 70620  
AAAAGAGTAA CATTCAATTAT AGTGTTTCTT TACGTTGTTG AAAATTTTAA ATCACTTAA 70680  
CATTAGATTT TTATTAAGC AAAAATATGT TTTCTTATT AGCTTACCCT TTTGTAAGTC 70740  
AGATTAAACC CTTGATTGTT CAAATTAACC TGAAAAAAT TATTCTTTTG GAGGCCAAAC 70800  
TTTTGATTAA GTAGTTGTTT GTCTCTAATT TTTCAAATT TATGTGTATA AATATAACCT 70860  
GTCATCAAAT CAATGCTAAC ATTCTATACA TGTTTTTCAT GATATGAAAA CTATAAAACA 70920  
TGAAGTTATT TGAATTTGTG TAGTTTTTAT CATTTTATTT TTACTTTCCA GTGCATCTAT 70980  
CCTTTGGGCT CTAAATCACT TAATAACCTA ATTTCTCCTG ATTTGGAAGA ATGTCACACT 71040  
CCACATAAGC CTCAGAAAAG GAAGAGCTTA GAAAGCAGCT ATAAGGATTC ACTTCTTTTA 71100

FIG. 6.27

GCAAATTCCA AAAAGACTAG AAATTATATT GCTATTGACG GTGGAAAAGT TTTGAACAGC 71160  
AAACATAATG GAGAAGTATA TGACGAAACC TCGTCAAAC TACCTGATAG TAGTGGTCAA 71220  
CAGAATCCAA TTAGGACAGC TGATTCTTG GAGCGGAATG AGATTTTGGA AGCTGATACT 71280  
GTTGACATGG CTAATAACAA AGATCCTGCT ACAGTTGATG TCTCTGGAAC TGGCAGACCT 71340  
TCCCCTCAAA ATGAAGGATG TACATCTAAA CTGGAAATGC CACTGGAGAG CAAATGTACA 71400  
TCATTTCCCC AGGCTTTATG TGTCCAGTGG AAAAATGCTT ATGCTCTCTG TTGGTTAGAC 71460  
TGTATCCTGT CAGCTTTGGT GCACTCGGAA GAGTTAAAGA ACACCGTGAC TGGACTGTGC 71520  
TCGAAGGAGG AATCTATATT CTGGCGGTTG CTTACAAAAT ATAATCAAGC AAATACACTT 71580  
CTATATACCA GTCAATTGAG TGGTGTTAAA GGTTGGTACT AATATTTTAT TTTTATTTAC 71640  
TTATTTATTC ATCTGGAGTC AGGGTCTCAT TCTGTCACCC AGGCTGGAGT GCAGTGGCAT 71700  
GATCATGTCT CTTGTCAGCC TTGACTTCCC TGGCTCAGGT GGGCCTCCCA CCTCAGTCTC 71760  
CCAAGTAGCT GGAATAACAG TCGTGCACCA CCATAGCCAG CTAAGATAGT GAGATGGTGG 71820  
CCCCACTGTC TTGCCAGGC TGGACTCGAT TTCCTGGGTG CAAGCACCTT TCCCGCCTCA 71880  
GCCTCCCAAA GTGCTGGGAT TACAGGCATG AGTCACCATT CCAGCCTACT TGTCTTTAAT 71940  
TCTTAAAAAT ATTAATGTTG AGTTTGTCT CCCAGCATGT GGGAAAGATG TCATCCATTG 72000  
CTTCTGTTTC CTGGAGGCCT GGGAGCAAGG AGCCAGGAA CAGTATCACG AAGCTTGAGA 72060  
TAATACCAGT TACATTATCC TGAATGCCCC AAAGGCAGTT TTTTGTGTTT TTTTGTGTTT 72120  
ACTTTAAGTT CTGGGGTACA TGTGCAGAAC GTGCAGTTT GTTACATAGG TATACGTGTG 72180  
CCATGGTGGT TTGTTGCACC CATCAACCCG TCACCTATAT TAGGTATTTT TCCTAATGCT 72240  
GTCCTTCCCC AACCCCTCCA TTCCCCATCA GGCCCCAGTG TGTGATGTTT CCCTCCCTGT 72300  
GTCCATGTGT TCTCATTGTT CAACTGTAC TATGAGTGA GAATATATGG TGTTTGGTTT 72360  
TTTGTCTTGT TGTTAGTTTG CTGAGAATGA TGGTTCCAG CTTTATCCAT GTCCCTGCAA 72420  
AGGACATGAA CTCATCCTTT TTTATGGCTG CATAGTATTC TATGGTGTAT ATGTGCCACA 72480  
TTTTCTTTAT CCAGTCTATC ATTGATGGGC ATTTGGGTTG GTTCCAAGTC TTTGCTATTG 72540  
TGATTTTTTT TTTTTTTTTT TTTTTTTTAA GACAGAGCCT CACTCTGTTG CCCAGGCTGG 72600  
AGTGCGATGG CATGATCTCA GCTCACTGCA ACCTCCGCCT CTCAGGTTCA AGCAATTCTT 72660  
CTGCCTCAGC CTCCAAGTA GCTGGGACTA CAGGCGCCCA CCACCAGGCC CAGCTAATTT 72720  
TTGTATTTT AGTAGAGACA GGGTTTCACC ATGTTGGTCA GGCTGGTCTT GAACTCCAGA 72780  
CCTCATGATC TGCCTGCCTT GGCCTCCCAA AGTGCTGAAA TTACAGGTGT GAGCCACCAT 72840  
ACCTGGCCTA GGCAGTCTTT TTCAAAACTA TAAGACTGTG CTTGTGTCTC AGGGTGTGAG 72900  
GATAATAGTG GTTAGTTTAA AGTGTTTAAA CTAATGAAAA GCAGAATGAA GAAAGTGAAGT 72960  
AAAATCACCC ATAATCACAC AACCTCCTAA GATCTCTTGG CACAATAAGG GATATGTTTT 73020  
TCATTTTATT CTCTGTAAAA TAGGATACTT ATGAACCCAC CTCCAACAC AGGAAGAATT 73080  
AAAACATTCC CAATAACTTA CATTTACCTA TGCCTTTCCT CCCATCCCAT TCTCTACCTC 73140  
CCCCCATATA GTAATCATT TCTGAAATGT GTTTCATCAT TCCATCTTTT CTTAGTTTTT 73200  
CTTACATGTG TTTATCTAAA CAGTATACAG TAGTCTCCCC TTATTGTAGT TGTACTTTTC 73260  
TTGGTTTCAT TTAACCCGAG GTCTGAAAGT AGATGAGTAT AGTACAGTAA TATATTTTGA 73320  
GAGAGAGGGA GACCACATTC ACATAACTTT CATTACAGCA TATTGTTATA ATTGTTGTAT 73380  
TTTATTATTA GTTTAATCT TACTATGCCT AATTATAAAA CTGATCATA GGTATGTAGT 73440  
TATAGGAAAA AGCATAATAT ATAAATGTT TAGTTACTAT CCAAGGTTTT AGGCATCCAC 73500  
TGGGGTCTTG GAAGGTATCC CTCTCAGATA ATGGGGGATG GATGGTACTG AACCTGTAT 73560  
ATACAATGTT TTTCCCTATA CATACTAAT TATGATCAAG TTTAATTAAG AGTAAATTAA 73620  
ATGTGGGCCA GGTGCAGTGG CTCACATCTG TAATCCAGC ACTTTAGGAA GCTGAAGCGG 73680  
GCAGATCTCA TGAGGTCAAG AGTTCGAGAC CAGCCTGGCC AACATGGTGA AACCCCATCT 73740

FIG. 6.28

CTACTAAAA ATACAAAAAT TGGCTGGCTA TGGTGGCACA CGCCTGTAGT CACAGCTACT 73800  
CTGGGAGGTT GAGGCAGGAG AATTGCTTGA ACCCAGGAGG TGGAAGTTGA ACAATCACTT 73860  
GAACCTGGGA TCACGCCACT GCACTCCAAC CTGCCTGGGT GATAGAATGA GACTCTGTCT 73920  
CAAAAAAAAA AAAAAAAAAA AAAAAGTAAA GTAAATGTGG CTCAACATGT TGCTGTCAGT 73980  
TGGAACATTT GTTCTGATC GTGTCTTCCA CCCACAAATT GAATGCTTTT TCCATCTTAA 74040  
CACTTATCAG GCACTGTGGC CATAACTTGA GCAGTTGAGA TGCAACAGCA AAATTAGCAC 74100  
AAATTTCTTT TTCTTTCTTC GCAGTTTCAT GGATAAGAGA TTTGTTCTTA GATCTCAGCA 74160  
ACCTCAGCAT ATGATTTTTT TCTTAAAGTT GAGAACTTTG ACCTTTTTAC TTAGAGAAGC 74220  
ATTTTACAGC TTCTCTTTGG CATATCTGAA TTGCCAGCAT TACTATGCTC GTGCTTTGGG 74280  
GCCATTATTA AGTCAAATAA GGGTTGCTTG AACACAAGCA CTGCAATACC ATGGCAATAG 74340  
ATCGCATCAC CAAGATGGCT GCTAAGTGAA CCACAGGCAG GAGTGTAGAC AGCATGGACA 74400  
CATTAGACGA AGGGAAGATT CACGTTGCCA GTGGAACACA GCAGGACAGC AAGAGAGTTC 74460  
ATGATGCTAC TCAGAAATGGC ATGAAATTTA AAGCTTATAA ATTGTTTCTG GAATTTTCCG 74520  
CTTAATATTT TCAGACCACG GTTGAGTTCA GGTAAGTGAA ACCATAGGAA GCAAAACACG 74580  
GATGAAGAGG GACCACTTCG TATTGCCTAA TTAGTTTGT TTTGATCTTC TGGGACCTTT 74640  
TTTTCTTGTT GTAAAAATT ATGGGGCTGT TTATAGTTGT GGCTCATTGA TTTTTCATTG 74700  
CTACATAATA CTTCATTTT GTAAATATAA CAGAATATTC ATCTACCTGT CAGTGGACAG 74760  
TGGGGTTTTT TTGCCATTAT AAATGCTGCT GCTGTGACCA TTTGGGGGGC AAGTCTCCTG 74820  
GGGCACAGTA TGAGTTTCCC TTCTGTATAA CAAAGGAATG GAAAATTATA GACTTTCGTG 74880  
TCCAAATTTA CAAGATAATG ACAATTGTTT TCCAAAGTGG TTGTACCAAG CAATTCTCCC 74940  
ATTAATAGTG TATATAAGAG GTCTTCCTGA TCCATATATT CTCTTGTT TATTTTCACA 75000  
CTTTTGAGAT TTTTGCTATT TGAGTGGTAT AAAATGGTCT GTGATCTTGA TTTGCCGTTT 75060  
CCACATTTTG AAGAGGTTGT CGGCTCTATG TGTATATATT GCTCATATTT GTTCCCTCTT 75120  
CTGTGAAATG CCTTTTGTAT CTTATCCCTA TTTGTTCTGT TCTGTTGATT GTCACGTTTT 75180  
AATTGATTTG TATGAGTTTG TTCCTTGAT CATTGTTGCT AGAGTTACAT CAGATGTGTT 75240  
GCTGAATCTG CTCCCAGTTT GCAGCTTGTG TTTTACTTT TAAAAACTG TCTTGATTTA 75300  
TAGGGAAGTC TTTATCTTT CATTTGGAGC TAGTAATGTT TGTGGCTTTT TAAAGAAATT 75360  
ATTACTATTC CCAAGGTCAG AAAATCATTC ACCTATATTT TAACTGAAAA GTTATAAAGT 75420  
TTTGCTTTTG ACATTGAAAT TTCTCATTCA GTTGAATTC ATATTGATGT GTGGTATGAG 75480  
GTAAGGATCC ATTTTTTTCC CATTTGCATA GCCAGTTTTT GTAGCTCCAC TTTATTTTCT 75540  
CACTTGATCT GCCATGCCAC CTCTAGCATG TATCAACATA TCATGTATGT GTGCAGCTGT 75600  
TCCTTAACTC TCAATTTTAT TCTCTTGGTT ACTTTGTCTA ACCCAGCACT CATACTTTTT 75660  
AAATTATTAT GGCTACCTTG TAGGGCAAGA ATCCTCACTT TTATTCAACT TCTTTTGAAG 75720  
TGTCTTGATG CATATTTTT CTGATCTTAC TTGGCCATAT ATATTTTGGG GACAGATGTG 75780  
ACATCATACC AAGCTTTCTT TGCTTGACAT TGTAGATATT TTCTTATTCA TTAATGTGCT 75840  
AAAAATTTTG AGTTTGGTCA TACAGTCTTT TATATGGATC TTATACATCG TTTCCCTCTT 75900  
GTTAACCATT CAGGCTGTTA CTAGTTTTTG CTGTTGTGAA TTAACACCAG GACAAATATC 75960  
CATATATCTT TTGAATTAAT TACTGACTAG TTTCTAGGA AAGATATTAG AATATGAATA 76020  
TTAAAGGTCT TGCTGAATAC AGTTTTCAGA ATGGTTGTAC CAATATATAA TTCCATTTTC 76080  
ATTATGTAGA AAAAATACCT CAGTGTTTTT TAACCACCTT TGGTTAGAAC ATTCAAGACG 76140  
TTATGGTTTT GTTAGGTAAG AAATATTTTG TTTCAAGTGA GGTTTTCTTT GAGACTGAAC 76200  
TTTTTGTGT GTGTCAGTCA TTTACAGTTT TTGCAATTT TAAAAATTCA GTTTCTCACA 76260  
AGCATTTTGC CTTTGACTTT TCTTCTATTT CTGCTTCTC TAATTACAGA AACCCCAGTG 76320  
TTAAGTAGGT GACAGTTCAG TTGTTTGCTG CAGAAGAGCA GCAGTTCAAT ATTGGAATTA 76380

FIG. 6.29



ACTTTAATTT TATGTTTTTA ATCTGTTACT AATTTTTTAC AGAATAATTG TAGTTTTTAT 76440  
AATCTGGTTA ATTATATGTT TGAGCTGCAT TACTTTGCAA TGTAAGTTTT TTTTTTTGGC 76500  
ATGGTCAAAT AACAAAAATT CTGGTTAATG CTTATTTTCAT ATTACAGGAG AATCCAGATA 76560  
TTTCATTAGG GAAACATATA AGCAGAGTGT GATCAGGCTG TATGAATTAT TTATAAGAGA 76620  
TGTGAGTGAA AAGATCTATT TGTAGCTTAA GAGTAAGTAG AGTCAGATGC ATGTAGAGTC 76680  
TTTTATTCAA AATAATTTTC TTATTAATCT TGGATAGTTT CTTGTCACAG TAATTCCATT 76740  
TTGAAGATAA TAAATATTAC CATAAAGAAG TGATCAAAAA CATAGATATG TGTGCCCAAA 76800  
GGTATTTATC ACAATAGTAT TTATAAGT GAAAAAGAA ACAACTAAAA TGCTGGCAA 76860  
TAGGAGAATG ATTAATAAAG CGATGTTTCA GCTGAATATA GTGGCATGCG CCTGTAAGCC 76920  
CAGCTACTCA GGAGGTTGAG GCTGCAAGAT GGCTTGAGCC CAGGAGTTAA TGACCAGCCC 76980  
AGGCAACATA GCAAGACCCT GTCTCCAAAC ACACAAACAC ACACACAAGT GCTATGTTTC 77040  
AGTCACTGTA TAATACTAG CCAGATTTTT TGTGTGTGTT GTTTTGTGTT TGTTTTGT 77100  
TTTTGAGAGA GCATCTCACT TGCCCAGGCT GGAGTGCACT AGTACAATCA CAGCTCACTG 77160  
CAGCTTGTAG AACCTAACC CTCCTGGGCT CAAATGATCC TCCCACCTCA GCCTCCTGAG 77220  
TAGCTGGGAC TACGGGTGGG TACCACCATA CCCAGCTTTT TTTCTAAGAG ATAGGGGTTT 77280  
CACTATGTTG CCCAGGCTGG TCAGTTTTTA ATGAAGCACA TTTGTGTAGA CAAAGCAGGA 77340  
TGTGGAACCG GATAAACACT ATGTTGCCAC TGAAGACCCC TTCAAACCCC TCAAAAATGA 77400  
CATAGAAGGG AAATATGAGA TATTAGTTTG GGAAATAATT GTAACTTTAT TAAGACTCCT 77460  
TATAAATTA TCTGTTCTTA TGACCTGGCT AAGTTCAATA AAAGTTACAC AGAGTGGAAT 77520  
AAATGGTTAG ACATCATTTG TAGTATAAGT AATTGCACAT AAGGAGGTAA CTTTAGCTGT 77580  
TTTAGAGATA GACATAGTAT CTGAAAGGTT AGTTATTTTA CTAGACCTGT GATTATTTGG 77640  
GTGAGAAAGG CTTTCACTGA GATTTTACCC ATTCAGTAAG TACTAATGAT ATTGTGCTGA 77700  
TAGCATATAT TAAGGGAATA TATGGTATAC CACAGAGAAA GAATTAAGGA AATTTTGTGT 77760  
TTTGCTTTT GTCTGTTGC AAACTTACT GACTCAGCTT TCATTCTTGG GAATGTGTCA 77820  
GTTTTCTGTG GGAAGATATA CATTGATGAG GAATTGATAA TGTTCTCTGT ATTTTCTTAG 77880  
ATGGAGATTG TAAAAAATT ACCTCAGAAA TATTTGCAGA GATAGAGACC TGTCTGAATG 77940  
AAGTTAGAGA TGAAATTTTT ATTAGCCTTC AGCCCCAGCT TAGATGCACA TTAGGTAAGT 78000  
AATTGGTAAA ACTTACTTGT ATTATACTCA TCTACCATAT AGAAATATGT ACCTCATAAG 78060  
GAAATATAAT ACTGTTTGAT TACCTTGGAT GATCATATTC TTGGGAGAGA GAATCTGAGT 78120  
AGTTTGACTT AGGAATCTAC CACTGGGTAA GTTATTGTAG GGCAGAGCTG TTCCATATAA 78180  
ATATGTAGGC TGGTGTCCA CCTCTTGAGA GTGGGTGCAG TTCTCAGAAC CAGGAGAATT 78240  
TTAGGGGGCA TATCATTAGT TGCTTCTCTA GTACGTTTCC TAGTAGACAG ATCTAGCATT 78300  
TTTAACCTCA ATTGTGCATT AAAAAGCACC GAGGGAATTT AAAAGTAAAT GCCAATGCTG 78360  
GGGCATTTGA ATTAGGATCT CAGGGATGGG GCTCAGGAAA TCAGTAATTT TTAGAAACCC 78420  
CACATGATTG TTATATGTAC CCAGGGTTTA GAATCTCATC TAAACCAACC ATAGTAATTC 78480  
TACTTCCCTA CCAGTGATTG GTTTAGGAAT GTCCTTGTGG TAGAGTTTTG GCCAGTGGAT 78540  
ATTAAGAGAA ATATGCTGAT GGCCTTTTGG GAAAGCTTCC TCGCCTTAG AAAGGGCACA 78600  
AGGATGGGAC CTCTTTGTTT TCTGTGACTT GGTTTTTGGC CTGTGGGAGT GCGTGCAGC 78660  
AAGTGAGCTA GAGAGTCTGT CCAAACCTTT CTAAATTTTT TTAGTATTGC GAAAAGGAGC 78720  
TGCGGGGTTT TTTTGTGTTT TTTTGTGTTT AAAGGGCTTT TTGTTTTATT TTTCTTGAT 78780  
CCTTGATTA ACTCTTCTAT TAATGTTATA GTAGCAGAAT ATGATACTCC CTATTAGTAA 78840  
TAACCCATAT TATGTAAAT ATCAGTGCCT TCTAGTTTTT CTCTCAATGA GTGACATTTA 78900  
ACTTATATTA AAAAATGATA TTTATATTTT ATAATAAAAT CAGTTGTTGC TACTGATTTG 78960  
TCTAGCATGT ACAAAGACA CCATGCTTCC AGATCATTAT AAAATATGAT ATTTTATAAT 79020

FIG. 6.30

ATATTTACAA TATATTTATA ACATATTTAT ATACTTAGAA TATATTTTAT AAGGCTGGGC 79080  
TTGGTGGCTC ATGCTTGTA TCCCAGCACT TTGGGAGGCC AAGGCAGGCG TATCACAAGG 79140  
TCAAGAGATT GAGACCATCC TGGCCAACAT GGTGAAACCC TGTCTCTACT AAAAATACAA 79200  
AAATTAGCCG GCGTGGTAG TGTGTGCCTG TAGTTCCAGC TACTCGGGAG GCTGAGGCAG 79260  
GAGAATCGCT TGAACCTGGG AGACAGAGGT TGCAGTGAGC TGAGATCACG CCATTGCATT 79320  
CCAGCCTGGG GACAGAGCGA GACTCCGTCT CAAAAAATGT ATATATATAT ATATATATAT 79380  
ATGTGTGTAT GTGTGTGTAT GTGCGTGTGT ATATATATAT ATCGGGAAGC ATGGCATCTT 79440  
TTGTACATGC TGGACAGCTT TTGACGACT TCTTTGACTC ATGCTTCTGC CCCCTAATTT 79500  
TCACTTTTTT TCCTACATT TATTAAAATT AATATATAAT AGTTGTATAT CTGCTTTATT 79560  
TTTCATGGAC TTATACATAC ATATTTATTC TGTTCTTATA AAAGTCTGAT TTTTCGTATG 79620  
CCAAATTTCT GACATTTCTT CCTCTAGGCC TGAAGAACTG TTGTAATTTA TGCATCAGAT 79680  
AGGCCCTCAG ATGGAATGAA TATTCTTTTT TCTTTATATC AAGGTGTAAT TTACATATAG 79740  
TAAGACCGTT TTTAAGTGTG TACAGCTCTG TAACCCTCAC TACAATCAAG ATATAGGACT 79800  
CTGTCACTCT AAAACTTCTC ACCAGGTTCA TCACCCCAG CCACTGATCT GTTGAGCGAA 79860  
TACTCATTTC AAAGGAGCTT TTTCCGTAAG ATCCCTAGAG TTTAGATGGA AGGGCTTTCG 79920  
TGGTGCATTT AGCAGATACC ATTTCCCTTC TAGACTCCCT ACTTCAGTTC CCAGTGAAT 79980  
TAAAGAATGG TTTCTCCCC AGCCTGAGTC ACTACCTTC TTATCCCTGA TAATTATTTT 80040  
TGGAACAAAG TTACATCTTT TGCTCCACCT CCGCCATGGG CCTGGTTTTT TATGTAACAG 80100  
AAGGAATTTT TAAATTATTG TTTTGTGTAA TCATAATAAT TGGGCAAGCA TACAGCTCTT 80160  
TTCAGTGCAG GAGGATTCCT CTCTTGTTTT ACTGCCATT CAAGGATAGG TGCTATATTT 80220  
TAGCTGAAGA TCTACTAAT GAAATGCTCT GTAATCATAT AACTTATTTA AAGATGTGTT 80280  
TTGAGCTCTT TCATAATATT TTAATTCATG GAGAACTTTA TGTATTTTAG ACCTGAAGAT 80340  
TTTATATTGT CATTATGAAA TGTAAATTGT TTGCTTTTTT AGTTAATATA TAGTTACAAT 80400  
AGAATACGGA TTTAAAGGCT GATAATGAAT TACAAAATTG TGCTATATGA CATACTGTTT 80460  
ATGCATACAG TGTTGCATAT TTTCATTTCT AGGATATTGA TTTGTATTTT TACTTACAAA 80520  
AAAACTTTTT AAAACTTATT TTATGGCTGG GCCCGGTGGC TCACACCTGT AATCCCAGCA 80580  
CTTTGGGAGG CCGAGGCGGG TGGATCACCT GAGGTCAGGA GTTCAAGATC AGCCTGGCCA 80640  
ACATGGTGAA ACCCTGTCTC TACTAAAAAT AAAAAAATT AGCCGGACGT GGTGTAGGTG 80700  
CCTGTAATCC CAGCTACTCG GGAGGCTGAG GCAGGAAAAT TGCTTGAAC CAGGAGGCAG 80760  
TGTTGTCAGC GAGCAGAGAT TGCGCCATTG CACTCCAACC TGAGCAACAA GTGCGAAACT 80820  
CCTTCTCAAA AAGAAACAAA AAACTTTTT TTAATGTTTT TGTTCAAAG TAGCAGTGAG 80880  
ACTATCCCGC AAAGGTGACT ACTAAAATAG CCTTTGTAAC TACTGATATT TATAGAATAT 80940  
GCTTAGGGTT AGGGTATAAC TCGCTTGAT TATACTCATC TACCATGTAG AAATATGTAC 81000  
ATCATAAGGA AATATAATAC TGTTTGATTA CCTTGGATGA TCATATTCTT GGGAGAGAGA 81060  
ATCTGAGTAG TTTGACTTAG GAATCTACCA CTGGGTAAGT TATTGTAGGG CAGAGCTGTT 81120  
CCATATAAAT ATGTAGGCTG GTGTTCCACC TCTTGAGAGT GGGTGCAGTT CTCAGAACCG 81180  
GGAGAATATT TAGGGGACAT ATTGTTAGTT GCTTCTCTAG TACTTTTCCC AGTAGACAGA 81240  
TCTAGCATTT TTAACCTCAA TTGTGCATTA AAAAGCACCG AGGGAATTTA AAAGTAAATA 81300  
CCAATCATAG GGACATTTGA ATTAGGATCT CAGGGAAGGG GCTCAGGAAA TCAGTAATTT 81360  
TTAGAAACCC CACATGATTG TTATTGCTTA GGTAATAACA CCTACTGTCT ACCTTGTTGGT 81420  
CCTGCCAAGG TGAAGTTCC TGGCCATGTT CCAGGCAACT GTAGTTCCAG GCTAGGGGGA 81480  
GAACTGGACC ATGGAAGTGA GGCTCTGTCC AGGGTAGGGG AAGGGATGGA AGGTGACTGT 81540  
TCCTGGCCAT GTTCCAGGCA ACTGTAGTTC CAGGCTAGGG GGAGAACTGG ACCATGGAAG 81600  
TGAGGCTCTG TGCAGGGTAG GGAAGGGAT GGAAGGACTC AGTCTCTTGG GCCAAATCGG 81660

FIG. 6.31

TAAGGCAGCA TCTAAGCTCC TCTGAGAATA GGAAGGAGAG CAACCAATTG GAAAAAGAAT 81720  
GGGAAACATG TAGATTCTCC TGCTTACCTT ACTTTCCAGT CTCAAAGCTG GAAGCCAGCA 81780  
TTCAGTGTTT AGTTATTTTC AATGACAACA AGATTCAAAT CTTAGTTGT AAAGTTGTTA 81840  
AAGGAAAGGA TTAGACTGAA AAGTTAAGAA GAACGGTAGA TGAAGAGTCC AAAGAGTTGA 81900  
GGCTGGTCAT TTAACCATTG TGTGGCCACG CCCTCTCCAC AGGTGGAACA AGATGATCAG 81960  
AATAGAAATG GCCAATTCTG ATGTGTTTCT ACAGTGTTC ACTGATTACA TTTTAAACA 82020  
TCTGTAGCAA ACCATTTCCA TAATTTTTTT TTTTTTTTT AGAGACGAGG TCTCGCTCTG 82080  
TCACCCAGGC TGGTATGCAG CGGCATGATC ATAGCTCACT GCAGCCTCAA ATTCCTGGGC 82140  
TCAAATGAGC CTCCTGCCTT AGCCTCCTAA GTAGCTTGA CTACAGGTGT GTAGCACCAC 82200  
TCTCAGCTAA TTTATTTTCT TTTATTTTT GTAGAGATAA TGCCTCGCTA TATTGGCCAG 82260  
GATGGTCTCA AACGTTTATA GAACTGGTT TTAGGTTCT AGAGGCTGGC AGCAATTCTC 82320  
AGAGGTAACG CAAGCAGTCT TCCTGCCTTG GCCTCCAGT GTGCTGGGAT TACAAGGTGT 82380  
GAGCCACCAC ACCTCATCAA TTTTGTTTT AATATACTCT AAGGCTTATC ATAGTTCCGA 82440  
GATCTTTTT TTTTCTCTGA GAAATCTAGA AAGATGGAAG ACAGTATGGG TCTTTGTGG 82500  
ATTTTTGTC CTAAGAAAT TTCATAAATG TCTGCCAAGG AAAAGGAAAG AGATCAAAGT 82560  
GGTAATTAAT TCTTAGGAT GGACATTTTT AGAAAAATGC TTTATAAACT TCCCCTCTCC 82620  
CAACTCTGAG TGACTTATTG TGTCATACTG TATTAACACA TATTCATGCT GTAAATATAG 82680  
TAAGAAAAGA CAATAGTTCA CAATTTTGGT TTAGTTTTG CCATTATTGA TTATGAGCAG 82740  
TAATTCTTCC TTTTCTTTTT GAAGGTGATA TGGAAAGCCC TGTGTTTGCA TTTCCCTGC 82800  
TCTTAAACT AGAAACCCAC ATTGAAAAGC TCTTCTATA TTCTTTTCT TGGACTTTG 82860  
AATGTTGCA GTGTGGACAC CAATATCAA ACAGGTTAGT TTCTTTGTT TTTTAAATG 82920  
GGTCTTCTA GTTTCTCCAC CACTAAGGT AAGAGAACA TTTGAGCACC AGACACTACA 82980  
GTTTGCTTGC TTCTTTAAAC TGAAGGGTC AAAACCTCAT CGTTTGATAG ACTGCTAGTA 83040  
GGATATTTCC TAAGGAGTTC TTCAGTGGGA AATAGGGACG ATGAGAGGAA TAATACACCT 83100  
CCCTCTCCA GAGTCTTGC TGAGTAGAAT ACCTCTCAGA ATGCCATGAA ACTGTAGGCA 83160  
TTTTGTTA TTCTCTATT AGAAATGAGG GGTGTTGCTT GTTACTTTA GGTTCCTAAC 83220  
ATTATAGACA CTAGTTTTAG GCTCTGGAG GCTAGCAGCA ATTCTCAGAG GTAATGCAAG 83280  
CTTCCCAT TCTTCCGTA GTCCTGTGAA AGACCAGCCA CCTCCAGAAG CCTACACATG 83340  
AGTCTTCTCA GCCATACTTT CTGCTTTTCC TAATGCCTCT CAGCAGCGTA TTAGAAAGGC 83400  
CATGATCGAT GTACCTGTTA CCTTCAGGCT TTGCATAAGG TGTATATGAA ACATAATGAA 83460  
TTTCGTGTTT AGGCTCAGG CCCATCCCCA GTTACCTCT TTATCTTGA GACACTTCTG 83520  
GTCCCATACA TTTCAGATAA GAGATATTCA ACCTGTACCC ACCACGTAAG GAGAGGAATA 83580  
GGTTTATGAA GAGGAGTCAG GGAGGCAAGG TATCCCAGA GGGATATTCT CACTTGGTCC 83640  
ATACCTGAGA AAGTTGCTGG CTGGCAGTTA GGAAGATGAC CAGACTGGCT CAATTGTTCC 83700  
TGTATCAAA TTATTACAAT AGAAATAACT CTTCCACCC CCCCCGCC TTTTTTTTT 83760  
TTTGAGTTGG AGTCTCGCTC CCGTCACACA GGCTGGAGTG CAGCAGCGTG ATCCCGGCTC 83820  
ACTGCAGCCT CCACCTCCTG GGTAAAGCG ATTCTCCTC CTCAGCTTCC TGAGTAGCTG 83880  
GGATTACAGG TGTGTGCCAC CACGCCCGGC TGATTTTGT ATTTTAGTA GAGACAGGGT 83940  
TTTGCCATGT TGGCCAGGCT GGTCTGAAC TCCTGACCTC AGGTGATCCA GCCACCTGAG 84000  
CCTCCACAG TGCTGGGATT ACAGGTGTGA GCCACCATGC CTAGCCACAC TTTCTTTAG 84060  
CTTAAGTGCT TAAGTTAGAA AACTTGAAG CTCTCTAAGT TACTCAAGTA AAATGTGAGA 84120  
TAAAAATATT ACTTTGAAG GCCGGGCACA GTGGCTCACA TCTGTAATCC CAGCACTTTG 84180  
GTAGGCCGAG GCGGGTGGAT CACGAGGTCA GGAGTTTGA ACCAGCCTGG CCAACATGGT 84240  
GAAACGCTGT CTCTACTGAA AATACAAAA TTAGCCGGGC ATGATGGCGG ACACCTGTAG 84300

FIG. 6.32

TCCCAGCTAC TCGGGAGGCT GAGGCAGGAG AATAACTTGA AACCCGAAGG TGGAGGTTGC 84360  
AGTGAGCTGA GATTGCACCA CTGCACTCCA GCCTGGTCAA CAAGAATGAC ACTCCGTCTC 84420  
AAAAAAATT AAAAAAATT ACTTAGATAT TCATTATCTA AATATGAAAT CCTTTTATAG 84480  
TATTTAAGGA GTAGTCAAGG AGAGTTCAGT CTGGGAGGAT GCTCCAGGGA ATGCAGGCAA 84540  
CAAAGGTTTT GTTTTTTTTT TAACTGGTTA ACTCAGATCT ACTAGAACAG GGTAAGGGAG 84600  
GCCACAGAGT AGACACCATG AGCAAAGCTA ACCCTCCTGA GTTGAAAAAA TTATGGACGA 84660  
GAAGTTATCA TTGAAATTAA CTGTTGGCAG ACATATCCAA AGAATATCGC AAGGATTTGG 84720  
TCCCTTTATG CATCCTGAGA CAGATGAATG TGTGGAATGG CAGCTGGTGG GCAACAGAGC 84780  
GATATTGGCA TGGTGGTGAT ACAGGGAAAT AGTTTCATCG TGTTAAAAGC CATGGAACAA 84840  
AGATACATAA TGGCTGCTCT GCAGAAAAAT CCACGTCCCC TCTCCAAAGG GCCTGTTTTA 84900  
CTCTGATGTA AAAATTGGGT CAGATAAATT TTCATATTAA GCTTTTTGTT GAGTAAACTT 84960  
TTGTAATAGT CCCCCAACT CCCACTAGAA CAGGGTGAGA ATTAACGTTT TATTCATACC 85020  
TAGGACTTAA ATAATTTAGT GTAAGCAAGT GAGTATGAGA ACACATCTGT TTCCAGTCTT 85080  
CTATCATTGC TTTATATAAA TTCTCTGGTT TTCTCCTCAC AGTAACTCAG TGAGGAAGAT 85140  
CCTAGTGTCC TCATTTGGCA CGTATGGATA TGACAGCTTG AAAGGGGTTA GATTGATTCC 85200  
CAAGATGACA CACTGTAAGT GGCAGAGTCA GGAGACACAC TTAGGCTCTT CTGGCCTCTA 85260  
AGACTTCTT GCTCACTGTG GTATACTCCT TAATCACTAC CTGGGTTTTA AATAATATAA 85320  
ATAACCTTGC TGATTAAAAT CAGCTTAATT GTAGCTTCTC TGGAAATCCAT ATCTTAGTTG 85380  
TTTGACAGTT TTCGGTTGAG TGTCTTCTGT GTGTTAGGAA CTCAGGCACT GGAAATAGTG 85440  
TATCTTTGCC AAATTTACTA ATTAGGTAGA GAGATAATAC ACGAACACAT AATAGAGGTC 85500  
CAGTGACTTC GTAATTAATC TGATCTTTGG GCTGCTTAAC GTTAGCTTTG AATGCAAGAT 85560  
GTTAAATGCG TTTTAGAGAT ATATAGCACA AACTGTGAGA GCTCAAGGGA GGAAGCCAC 85620  
TAGCCGCTTT TGTGCTTTT TTTGTTTTT AAAAAAATC TTAAGTTGTT CTAATAATAA 85680  
AAGTAGTTAT AGAGGGAAAG CTAATGAA GTGACGTTT CTTAAATATG TTTAATATG 85740  
TCATAACTTA AAAGTTATTT CCACTTAATC TGAAGGAGAA CTGTCCAGCA AATTCCTTTG 85800  
TTTTTGTA GCTGTTTTTA GTGCCAGCAT AAGGGCTTTT TACTCAACTT GGAAAGTGTA 85860  
ACCCAGAGTC AGTTAAAAAC ATAGTCTTCA GAGGCAGATC TCAGGTCTGT TATTTATCAC 85920  
TGACTCTAT GTGTCACCTT CCCCATCTGT AAAATGGGGA TAAGAATAGC ACCTGCCTCT 85980  
GAGAGTTGTT TGAAGATGA GTGTCCAGTG CCATGCCCTT TGCACATAGT TTAAGTGTTT 86040  
AGAAATGTCA GATGTCATGT GGAGAATTAA CACTTACTTG CTGAGACAGT CTCCTTTTTA 86100  
TAACTAAAC AGTAGGAGCC TTTACATAAC AATTATCTTT GAAAATTTAA GAATTTAGCA 86160  
GAAATCAGTG CATTTGTTGA TATCTTTATG TTGCTTTGCT TTTAAATGT TAACCTCCCT 86220  
GACTACTGAT GTTTTTAACA GACAGTGCTT CCTCACAAGA TTTATAAGTA TTTGCTATTG 86280  
TTTAGAAAGG AAGCTTGAT CTCTTAAGTA GCTGCTCTT AAATTACAAA TATTTTATT 86340  
AAAGTGATG CAGTTGAGGT TTAGTGATCA TCTTTAAAGG TCATCTTTT AGATGGCGTT 86400  
GCTCTCAAGT ATTCAGACTA AAGTGCAAT TTAGAACTTG TGTAACCTGT GAAAACAAAA 86460  
TTTGTTTACA ATTAATGCTG TGTGTGTGTG TGTTTTTTT TTAAGGATTA AAAAAAGTTA 86520  
AGTTGTATGT ATCCTGATT TTATGTTGG AACATCCCC TTTTCATTTT TGGTTGTCTG 86580  
TAATGGCTAG CCAGTTTGAG TTATTTGAGT AAGGGGTGAG CTCTTAATAA ATTTGACAAC 86640  
CTTAGAACAG TGGTCTTCA CTAAGGGCTA TTTTTCCCC CTTGGGACAT TTGGCAACAT 86700  
CTACAGACAA CTGGATGCCG TTAAGTGGAT CTGGTGAGGA GAGGCCAGGG ATGATGCTTA 86760  
ACATCCTACA GTGCACAGGA CAGTGCTTCA CAGCAAAGAC TCTCTGGTGA AAAATGCAGT 86820  
GATACCATTG AGGAACCCTG TCTTTTTTTC TTGCTTCATC TCATAGTTGA AAGATATGGG 86880  
AAATTAACAT GGAGCATCTT CACAGAGCTT CTTTACTAGA GGTAGGGAGG AACATTGCCA 86940

FIG. 6.33

TATTAACATG ATTTGGGGAA ATAAGAAAGT ATGAATCACG AAAAAGGGGA GGAATACTTT 87000  
TAGACATTGG TTTAAATTAA TGTAATGCA TTTAACGTTA ATGAATTGT TATGTCATTT 87060  
TTTTATAGGC ATATGAAGAG TCTGGTCACC TTTACAAATG TCATCCCTGA GTGGCACCCA 87120  
CTTAATGCTG CCCATTTTGG TCCATGTAAC AATTGCAACA GTAAATCACA AATAAGAAAA 87180  
ATGGTATTAG AAAAGTGAGT TAAAATTGTC TTATAATTTT TAGTACAAAA TGAAGGTGGA 87240  
TTTACATTTT TCTTAATGTG TAGGATTGAA AATGGTGACA ACAACTTACC TTTCTGAAAT 87300  
TTGAGTTAAC ATATATTTCT GGGTTGCCAG CTGCCTCGCT CTATCTGGCC AGTGAGCCCA 87360  
CTGTCACGGT GAAGCCACTG AAAAGCCAAC TTAGGCTGAC TCTCTGGCCC CACTCTCCTA 87420  
GTGTCTTTCC TTCTTTTTC CTTTTTCTC CCTTTAAGGA TATCAAGCTT CAGTTTTTCT 87480  
CTCCTCTGCC AAGTGTATGG AGTTTCTAGA ATTCTGGGAT TTCCTTAATC AGATTTCAAG 87540  
AACTAAGATG ATTCAAAGAT AAGCCACAGG CTCATCTCTC TGAATTTCCA TCTTCTCCTA 87600  
GATCTCAGCA TGCTAATTCC TCATCATCTT GAAAGCTATC TAGTGGCCTT GAGCAGATAT 87660  
ATTTTCATTG TATTTTGCCA GCTTTTCTGT TTGTCCTCAG TTGGGGAGGT TGGTCAGCAT 87720  
TACCTTTTCC AGTATTACCA GAGAACCATC TGTTTAAACT CACAGGTCAG TTCCATCTCA 87780  
GGCCGTTTCC CTCTGTCTCA TTAATGCACT CACACATGTA CACAACCTCT CTA CTCTTCA 87840  
TTTTCAGTCT AATCGTACAT TAAGGAAATG TTTTGAGGTC TAATTTGATG TAATAAAGAA 87900  
CCGGGAACAT TAACCTTTAT GCCCTTGAAT GTGCCAGAAA CCCTTCAGAA TCTTTCCTAA 87960  
AGGTTTATTC TCATTGAAGT AATAAATCCT CAGTTTATCA GTGCTTACAG GCTCAAAGG 88020  
GAAAAAGGGC AGTAGTCCCC TGTTCCCTCC TCCAGGTATC TACTTTAAAC CTTCAAATTA 88080  
AGGTAGTATT TACTTTTACT TTTCAAATTG ATGTGCCTAT TCTACCGTAA TGCAGTCTGT 88140  
TCTCCTTTTA TAGTAATTGA GACTAGGGT CTCACACCAA CACCTGGGCC CCATCTCTGT 88200  
TTAGCCTTTC CCTGTCTTT CAATGCAATT GCGTATTTGG CTA ACTCAGT ACTCGGTGTT 88260  
TGCATTGTTA TTAATATACA TGTGTTATTC CCTCTTCAGC CAAGCAGTAT ATATAGTTAG 88320  
GTTTCACTTT TACAATTCTT ATTTTCCGG GAATTGTTAT TTGCCTTGTT TCATTTGTT 88380  
TTATTATGTA CTGTGAGTTT TTGCCAATA CTTTAAAGAC TTATTAATAA ATTTTCAATA 88440  
CTCAGATGCT TCACAGTTTT TACTCTGTT CCTCTCCCCT TTTTTCCTG GAACTCTTTC 88500  
CTGCCACCTT TCACTCTTTG CTGCAGTCTG CGCTGGTTCC TCTCTGGGCC TGCAGCATAG 88560  
GGTGCTCTTT ATTATGTACA CACTTCCAGT CACTATCGTA GTTTTATAGCC CAAGGCCTCA 88620  
TCCCCACATT CTATCACATC TGTTGCCCAT AAATATCCAG TCCTTTAGGG GTTCTCTGGG 88680  
AAAAATAAGC TCTTCTTTGT CATCAACATA TGCCTCCGT AGTACTCATG TCTTCACTTT 88740  
GCCCCGTTCTG CTGGGTAAGG TGCCACTTCT CTGTTTGCTT TCTGTCTCT AAATATTTGA 88800  
CTTCTTATTT GCTTATTTTC CTTTCTTTGT CCTTTTGGAC TCATATCTTT TTTGCCCTC 88860  
ACTATTATTT GATAGCATTT GTGTAGGAGG GCGAAGTGGG AAGGAAGAGG AGGTGTCTGT 88920  
ATCTGTCTGA AGATTACAGA AGTCTGTAAT CTGTCTTGGC TGCCAGGTGT CAGTTTTGAG 88980  
ATGTAAATGT TGATGATGAG GTGAGGAGAA GAGCAGCAGA GCATGGGGTC TGCCATCCTG 89040  
CCTTGACCA TGGCCTGCTT TAGGCTGCTT GGTGTATATG ATTCATCTA GCTGTTCTA 89100  
CCTGCTTTTT CCTGTGCCCC AGCACTGAAC ATAGACTCGT ACCATTGTTT TGTGTAATCT 89160  
GTTAATTGGT TGCCTGTCAG CATATATATT TTTTAACTAT ACAAATAAGT TGCTTCCCTT 89220  
AAAGATTCAT GCTCTGATCT GGAAATGGAT TCATTAGGTA AAAGTCTTTT AATGGAAAAT 89280  
GTGTTTTGAG TTCCAGTGGG CCAATTTATG AGCAGAAATTT ATAATGTGGG CATTTCTGT 89340  
TTTCTTCAA AGTAAATTGA ACTAGTGTAT GAAGTTTAC TTAATTTTA AATGCCAAGG 89400  
TCTTATATA AGTCCTTTGT GTTTTTTAA TTTTGAAATT TGTATACTT GATTTGTTG 89460  
TGTCTAATGG AATTTAGAAA TAAATTTAAT ATAGTTTTTA GGGCTAACCT AAAAGTAATT 89520  
GGGTTCATCA TGGTGTCTA TGTAATTAAC ACATATAGAA TCCTAAAAAC TAATTAAGTT 89580

FIG. 6.34

CCTTGGACAC CTTATCTCAC ATAACCCACA TCTCTAATGT CTCCCCATTG GGAAAAGAGT 89640  
CCATTGATAA ATCAGGTGAA TTATGCCTAG CGGGCCCCAAA TCTGCTACTT TTCTTTAAGT 89700  
TGTTTAGGAG TTACATTGAG ACCATGGTGA CATGGAGCAC CAAGAAGTTA GAATCAGATT 89760  
TCATTTTACT TGACAACTC TTGAAAGGTC ACTGCCACAG TCTCTCTTGA GTGCAAGGCT 89820  
ATGGCTATGC TTTGTAGCAC AGGGACGCGA TATTTCTCTG CTATCTTTGG GTAGCAGAGG 89880  
TTAACACAGC TCCCTTGTGC TTTCTTTCTC TCTTTTCTAT TTTCTTTTCT TTTCTTAAGG 89940  
ATAGATCTTT AAATAGGAGG AGTTTAACCC CATGTTAGGT GAATTCAAAT GGATCTTAGC 90000  
CTGATGTCTC TTGTTCTCTT TTGGTTCCAG TTTGGTTAAT TCCTTTCATC CAATTTTCCA 90060  
GTGGTTGAGG GAGAACCTAA CTTGCTCTCC TCGACTCTGA GCATCATCCT TCACTGACAG 90120  
TTCAGGCATT GTGGGTAGGA AGAAGTCTGA GAACAAAACC TAGGGATAAA GTTTAGTAGA 90180  
GATGGGGTTT CACCATGTTG GCCAGGTTGG TCTCGAACTC CCGACCTCAG GTAATCCACC 90240  
TGCCTTGGCC TCCCAAAGTG AGGCTGGAAA TAAGACATGC TGGAAATTGTA AGTAGGACAC 90300  
TAGAGTCTAG GGGAATCAAA GAGGAAAATG AACAGAAAAG GGAAGGGGAA GGATATTATT 90360  
TGATTGACTC CAAGATGCTA CTGTTTGTA GTTTTACCAT TTTAAAAATA TGCCATTAAG 90420  
AAAGAAATGC TGGCCGGGCA TGGTGGCTTA TGCCTGTAGT CCCAGCACTT TGGGAGGCTG 90480  
AAGCGGACAG ATCACCTGAG ACTAGGAATT TGAGACCATC CTGGCCAACG TGGTGAAACC 90540  
GCATCTCTAC TAAAAATACA AAAATCAGCT GGATATGGTG GCACATGCCT ATTGTCCCAG 90600  
CTACTCAGGA GGCTGAGACA TTAGTACTGC TTGAAGTGGG GAGGCAAAGG TTTCAGTGAG 90660  
CAGAGATTGT GCCACTGCAC TCCAGCCTGG GCAACAGAGT GAGACTGTCT CAAAAAAAAA 90720  
AAAAAAAAAGA AAGAAATGCT GCTTATTTAA CTGTGTTCTG TCAATGTAA GGTGTATCCC 90780  
GACTTCAGAG ATGTTAACAA ATGGGAAAAA ATTTGGAATT CATTAGGCAT TTGGAACCTA 90840  
CAAAGTTTCG GCCGGGCATA GTGGCTCATG CCTGTAATCA CTTTGGGAGG CCAAGGCGGG 90900  
TGGATTACCT AAGGTCAGGA GTTCGAGACC AATCTGGCCA ACATGGTGAA ACCCATCTC 90960  
TACTAAAAAT AAAAAATTA GCTGGGTGTG GTGGCATGCG CCTGTAGTCC CAGCTACTCA 91020  
GGAGGCTAAG GCAGGAGAAT CGCTTGAACC CAGGGGGCGG AGGTTGCAGA GAGCTGAGAT 91080  
CGTGCCCTGC ACTCCAACCT GGACAACAGA GTGAGACGCC ATCTCAAAAA CAAACAAACC 91140  
AAAAAAAAAA AAAAAATTC ATAGTTACAG AAAGTAGTAT GGAGGCCATA CCGAGATTTT 91200  
CGACATGGTA GTAAACTCT GCATTATGGC TCTGTTCTGC ATCATCTCTG TTCTGCATCG 91260  
TTTCACTCCA CATCAGACCC TGGATAGCTT TGGTGTACTG GTCGATCTTG TGGCAGTAAG 91320  
GCTAGTGTA TTAAGAGGAT ATTTTAAAC TTAACATATA ATTGCTCTAG TTGTTGTCTC 91380  
TTTTTGTCTG GTTAAGAAAA TCAAATTTCT ATCCTATCTG AATCTCATAG CAGACTTTGG 91440  
AGATTTCTGA CAAGTCATTT CTTACTACCT AGGGGAATGT ACTTGTACTC AGCTAGAGTC 91500  
TGAGTATCTT CTACATCCAG GGAATTGGGC TGAGTGTGGA TTTTGGTCTT GGCAGTTTTT 91560  
ACTTTTATTA ATTTGCAAAA GAATAGAAGA CTTGGAATGT ACAAGAAGCA TAAAAATGTG 91620  
TCAGGTGGTT TTACATGCGT TATTTATCAC GTTAATATGT CTTAAGATAT TTTCCACGTG 91680  
TAACTTATG TAAAGGCAGG AAAGTAGTGA GATTTTCATAT TCTAGGGATC AAGAGATTGT 91740  
TTTAGTAAC AGCCTCAGAA AGTATCTTGA AAGGTATTAT ATAAGGTCAA GGAACATAAT 91800  
ATTAGTAAAG AGTCAGGCCA GCGTGGTGG CTTATGCCTG TAATCCCAGC ACTTTGGGAG 91860  
GCCAAGGCAG GCAGATCACT TGAAGTCAGC AGTTCGAGAC CAGCCTGGCC AACATGGTGA 91920  
AACCCTGTCT TTAATAAAAA TAGTAGTGTG TGGTATGGTG GCGCATGCCT GTAATCCAGC 91980  
TCCTCAGGAG GCTGTGGTGG GAGAATCACT TGAGCCAGG AGGCGGAGAT TGCAGTAAGC 92040  
TGAGATTGCA CCACTGCACT CCAACCTGGG TGACAGAGCT AGTGCTGTG TCAAAAAAAG 92100  
AAAAAAAAAA AGGTCAGATA GGTGCCTAAA GCCTGTGTGT CTCGCTATGA GAATACATCT 92160  
CAAGTTTAC TGTGGTTCAT TGATTCAGAC ATGTAGTTCA CATTTTAACC TGTCTGAAAT 92220

FIG. 6.35

GGTAATATGT GAAATTGATG TCATGATATA GTTTAATTGG CAGCATGTTT TCATAGTGGT 92280  
ACATTTTATA ATTAGTGAAA TCTTAGATTT GATGAAATAG ATATGATTTT TTAAGTGGG 92340  
AAAGTTTAGT GTTATAGACA GTTTGCAGGA CTTTTATTT TGTAGGTACT TAAATTTTGA 92400  
GGACTTAATT ATTCTCTAAT AAAGTGATTG ACAAGGATTA ATGTATAAAT TATACCTTGT 92460  
CAGTCTGAAC AATCTGCAGT TTGGACATTG ATTCAAATTC ATTTAGGCTG AATAAATTTT 92520  
GATAAACTAA GTAAGTTTTG ACAGCTATTT AAATATTGGG AAAGGGGATA TTCAACATTT 92580  
TTCTTACATC CTGAGAGCTT TGTTAAATTT AGTTATTTGA GACCCATTGG GTTCTATTTT 92640  
CTGGTTCAGC ATGTTGCTGT AATGGTAAAA TACAATTTTG AAATTATAGT TGTCTTGAAG 92700  
TTAATAATAA ATTGACCAAT ATGTTGTATT TTTTCTCTA CTTAGTTACA AATTGAACTT 92760  
TTCCTAAGTA GAACTTTTAA TTTGACAGGC CCCCTTGTCT TCCTGAGGTA ACTGAAATAG 92820  
GCCAAATTAA TGCTTTTTTG AATATCTTAG GTTTGTTGCT TTCTTTCACA TGTTACCTAC 92880  
CCCACTTAAC AAAAGCAATT AATCTCAGCA CTTGATGCCA AAGAAAATTC TAAAAGGTCT 92940  
GGATTTTTTC CTTGGATTTT ACAAAGTAGC TACAATGGGA CTTTAAAGAC AAAGCTGCAT 93000  
TGCTGCTTAC AGAGCAATTT TTGTTAATG GTCTGTGTTA GAGTCATACT GCATGATGAC 93060  
TTCCAACGTG CTGGGATACC ATTCTGAAAA GGGTTTAGTG TTACATACTT CTTAGAGAGA 93120  
GTTCTCCATT TCTAATTAAG GCACACATCT GGAGGTGCTC AAGAAAAATT AGTGCAGTTA 93180  
GCCTTGGAAG TGTTATGTGT GACTAGTTCA CTTGAGACAT CTTTGTATA ATCAGACACA 93240  
TGGCATTAAA TTTATTTAAC TTCTCTTGCT TTTCTCTCCC ACAGAGTATC TCCCATATTC 93300  
ATGTTGCACT TTGTAGAAGG CTTACCACAG AATGACTTGC AGCACTATGC ATTTCAATTTT 93360  
GAAGGCTGTC TTTATCAGAT AACTTCTGTA ATTCAGTATC GAGCAAATAA TCATTTTATA 93420  
ACATGGATTT TAGATGCTGA TGGTAAGTGT TTAGAGGTTT TCTTTAAGA TAATTGGCAT 93480  
AGAAACTAAA TTCTAGCATG TGGGGACTTT TTGGTTTTTG TTTATAAAAA AAAGACAAAC 93540  
TTTGTCTGA CTCTTTCTCT CTCCATTCTC GCCTTTGCCT TCTGCCCCCTC CTCGCATCTA 93600  
TTAAAAGTGA TGGTTTTAGT ATCCTGTCTC ATTTTTCCT TTCCTTACAT CATGTATTAT 93660  
AGGTAAACAC ATGCGCATGT GTGTATTTCT CTTTATAGACA AAGGATGAGA TTACTIONGT 93720  
TAGCTCAGTT TTTTTTCCC TACTTAACAT CTTTGCTTTT ATTTTATAGA CATATTTCTA 93780  
AGACTATTAA ACATTAGACT TACGTAGCCC TTCTGTCATT GTGAAATACA TAGTTTACTA 93840  
ACAGCTACCA TCAAGATAAA GCCTTTATTT AAATAATTAA ACTTCTTAGT GGAAAGCTAA 93900  
GTAAGCACAG TTTATGGATT TTGGGAATTT TTGCCTTGCA TTTGTCTGAT ATGGTAAAT 93960  
ATTGAGTTTG TTTTCTCAT AATGTTCACT TTGTCTTAGA CAAGATAACT CAATCCCCTT 94020  
AAAGGGTTGT ATCAAGCCAT TGATAAGGGC TCACTTTGAT ATAACCATT TCTGTTATTT 94080  
AGACACTCTT TCACACTTCC TATTTTCTC CTGGGGATGG TTTGAATGGA TGACACAATA 94140  
CCATATTATA AAAGCACTTT ACAAAGTGA ACTTATGTTA TAAATGTAAT TATTACCTTA 94200  
AGGTTTTACC CTGTTTCAGA TTTGAGTGGA AGTAGTTCTT TACAATACAA AACAACCTAT 94260  
TTTAACTTTT TTTGCATTTT AAAGAATGAT CAATCCACTT CAGGTGCAGC ATGGTTTCCA 94320  
ACCCTGACAG CATGGAAGAA TCATTTATTT AGCTTCTAAA AATGTGCAGG CTGTACCCTA 94380  
GACCAGCCTT GGGGATTAGG CCCAAATATC AATGTTGGGT GTTTTTGGTA TTGGTTTTTG 94440  
GCCCCCTAC CCGCCCTTCC TTCCTTCGTT CCTCTCTCTC ATTCTCTCTC TCTCTCTCTT 94500  
TCTCTCTCTC CTTCTTTGCT CCTTCATTCC TTCTCTCTCT CTCTTTTTTT TTTGAGACAG 94560  
CATCTCACTA TATTGCCAG GCTGTTCTCA AACTCCTGGG CTCAAGTGAT CCTCCTGCCT 94620  
CAGCTTCTG AGTAGCTAGG ACTACAGGCA CATGCTATGG CAATACTGTT TTAACATTG 94680  
TTTTCAAGGC TCCCCAGGTG ATTCCAGTGT GGGTCATGTG GTAGAGAACC ACTGACACAG 94740  
GCAAACAAAG GATACATAAA GTTGTCTATT TAATGGGTAG GTGCAGGTAG TAGATAAGAG 94800  
TGTAGCCACA TAAACCACAT GCTTAGTGAA CGGTTTTGTT TTGTGTGTAT GTGAGGGATT 94860

FIG. 6.36

AGCATCTCTG AGTATATTTT GTTTTCCCTT TTGAACTTA TCAGAGAATT CATATGTCTG 94920  
TTATGTGACT AATGCTCACA TTAATAAAG TTATGTGACT TTTTAAATT CATATGTCTT 94980  
TTTAATTCAT TTATTCATT ATATGTCTGT TATGTGACTA ATGCTCTCAT AAAAAAGTA 95040  
ATGCTCAGTT TACTTTTTT ATATCAGATC ATATATATAT GTTTTTTTTT TTGAGATGGA 95100  
GTTTTGCTCT TGTGCCCAG GCTGGAGTGT ATTGGCGCAG TCTGTCTCA CCACCACGTC 95160  
TGCCCTCCCG GTTCAAGTGA TTCTCCTGCC TCATCCTCCT GAGTAGCCGG AATACACGCA 95220  
GGCGCTACCA TGCCCGGCTA ATTTTGTATT TTTAGTAGAG ACAGGGTTTC TCCATGTTGG 95280  
TCAGGTTGGT CTTGAACTCC CAACCTCAGG TGACCCACCC GCCTCGGCCT CCCGAAGTGC 95340  
TGGGATTACA GGCATGAGCC ACCGCACCCG GCCATATCTT ATATTTAAT AAATATTTTA 95400  
ATTTGGTCTG TAAATTTTTC TTTTGGGGA ATGTGTTTTA AGTCTGTGTT GAGTCCTAGA 95460  
CATTTGTTGT TCTCAGATAG TCACTAGTGA TACCTAACA TTAACCAGCC TGTTGGCAAC 95520  
TAAATTGGCC TGAAGTGACA ACTAAGGAAA GGTCTCTTTC TCCTTTCTTA ATCTTTGCAT 95580  
TCCTTAAGAT TAGTTCTTG TAGGAAGGCT TTGAAGTCTG GTGGCAAGTA CCCTTTATCC 95640  
CTCACAATCT TAAGATAAGG TCTTCTGAG CATTAAAAAG TGAAGTGGG AGATATGTCA 95700  
AATGAGTTT CTGTGTGTGC TCTGAGAAAT CTTTTTTTCA AAAAAGGATA GATGTACTTG 95760  
TATAAGGAAA AGAGAACTG AGCGCACTTT CAATATTTAA GTAAGTGTCT CTAACATGTT 95820  
TTGCAACATA AAATGATGAC CACTGTGTTG GTCATTACTT CTCTACTGCT AAAACAATGT 95880  
TTTCTAAAAT AATATACTCC TTAGAAAAAA ATATAGTGCT TTGGGTGTGC ACTGTTGTAA 95940  
TCCAAGGAAT AGGAAATGTT TTGTAGTAAG TGCGATGGTG TTTGACATCG TGATTTATTA 96000  
ATTTATCACA TTTGGTTTCA TAGAAATAGA GTAAGCTACG TATTTGCTGT GCCGCAATTA 96060  
CCATGACATT ACACTTGAT CTATTTCTGT TTCATAGATG TGTAGATATT GATATATACA 96120  
GTGGAAGTAT GGATTGTTT GATAAGTTT TAATGAAAGT ACAGATATTT GTTGATTATT 96180  
TATTAAGAAA GGTGTTACT CATCCAAGCC CGTGGTTAGC TTTTCCCAA TTATCATGTG 96240  
GTAGTAAGTA AAATGTAAAG AAATATACCC TCCCTTAACC CCACACCACC TGTTAGCACC 96300  
TAGCCACCTT CCTTACTTC TCAGCCGTAC TTTTGTATT TTTTGTGT AGTGGTAAAA 96360  
TATAATAAC ATAAATTTA CCATTTAAC ATTTGTAAGT GTACAATTCA TTGGCATTGA 96420  
ATACATTGTG TGCAACCACC ATCACCATCA GGACTTTTTC ATCAACCCAA ACAGAACTA 96480  
CTCATTAAC AATACTCCG CATCCTTCCA CCCCAAAGCC CTGGTAACCA CTATTCTACT 96540  
TTCTGTCTCT GTGAATCTGT CTATTCTAGA TACCTCATAG AAGTGAATC GTACATTATT 96600  
TGTCTTTTG TGTCTGGCTT ATTTTACTCA GCATATTTTC AAGATTCATT TGTGTTGTGG 96660  
GATGTAGCAG AATGTCATTC CTTTCTAAGG CTGAGTAGCA TTGTATGTAT TATCCATTTA 96720  
TCTGTTACGG ACATTTGACT ATTGTGAATA ATGCTGTTGT GAACATTGGT GGACAAGGAA 96780  
CTGAAAGTCC CTGCTTTTCA TTCTTTTGG CATAAACCTA CAAGAGGAAT TGCTGGGTCT 96840  
TAACGGTAAT TCTGTGTTA ATTTTGGAC GAACTGCCAG ACTGTTTCCA CAGCAGTTGT 96900  
ACTATTTTAC ATCCCCACCA GCGTTACACA AGGATTCCAA TTTCTCTACA TCCTTGCCAA 96960  
CATTTGCTAT TTTCTATTTT TTTTAATAA TATCCATCCT AATGGGTGTC TTTTTTTTTT 97020  
TTTAAAGGAA TGGTTTAAAC AGGTTACCTT CTTACTCCTC ATTCATGCTT TAGTTGACTA 97080  
CATAAGGACC CCTCTCCCTA TTGGCACCAT TGAAATTGTT CAGGCAAAAA TAACTGCCAG 97140  
CGACACACTG CTTAAGTAA TGGACTTTTC CCAAGTTTG TATTAATATT TCAGTATTTG 97200  
GTAGTGCATC CTAAGTCTAG TTTTAAACT CTTCCCTTGT CATCTATCAT CTCATTCTCT 97260  
CTTGACAAAT GTGAAAATGG AAGCTCAGAA ATAAACAAG AATTAAAACG AATAGTGATC 97320  
CTTCAGGTAA CAAGCTTCAT TTATCATGAA AACATATATG TATGAAACAT TCTGTTTTCT 97380  
GATGTTATTG GATAAATTAG GTGATAACCA AATTCTAAGT TCCAAAAATT AAATATACTC 97440  
TATCTAAGGA CTTTAACATG GCAGACAATG GTGACAAGGT CAAGAACATG TTTTAGAGTC 97500

FIG. 6.37



TTCTCCTTTG GTCGGTATTC AATGATACAA CAGTTGAAAA GGCCAGAAGA AAGTTAACCT 97560  
AGGATGGTGG TTTTGAATA TCTAACTTTC ACTTCTTTCC CATCTTCCAG GAAGTTGGCT 97620  
GGAATGTGAT GACTTAAAAAG GCCCATGTTC TGAAAGGCAC AAGAAATTTG AAGTTCCTGC 97680  
TTCAGAGATA CATATTGTTA TTTGGGAAAG AAAAATATCC CAAGTGACAG ATAAAGAAGC 97740  
TGCCTGCCTT CCACTTAAAA AGACTAATGA CCAACACGCT CTCAGTAATG AGAAACCAGT 97800  
ATCTTTAACA TCGTGTTCCTG TGGGTGATGC TGCCTCAGCT GAAACAGCCT CAGTAACTCA 97860  
CCCTAAAGAT ATATCAGTTG CCCCTCGTAC TCTTTCACAG GACACAGCTG TAACTCATGG 97920  
AGATCATTTA CTTTCAGGTC CAAAAGGTTT GGTTGACAAT ATTTTACCTC TGACACTTGA 97980  
AGAAACTATC CAGAAAACAG CCTCAGTTTC ACAGTTAAAT TCTGAAGCTT TCCTGTTAGA 98040  
AAATAAACCT GTAGCAGAAA ATACAGGAAT TCTCAAAACC AATACTTTGC TATCACAAGA 98100  
ATCACTAATG GCTTCTTCAG TATCAGCTCC ATGTAATGAA AAGCTTATTC AAGACCAATT 98160  
TGTGGACATA AGTTTTCCAT CCCAAGTTGT AAATACAAAC ATGCAGTCAG TACAGCTGAA 98220  
TACAGAAGAT ACTGTAAATA CTAAATCTGT GAATAATACT GATGCTACTG GTCTTATACA 98280  
GGGAGTGAAG TCAGTAGAAA TTGAGAAGGA CGCTCAGTTA AAACAATTCC TTACACCAAA 98340  
AACTGAACAA TTAACCAG AACGTGTCAC ATCTCAGGTA TCTAATTTGA AGAAAAAAGA 98400  
AACTACAGCA GATTCTCAAA CCACAACATC TAAGTCATTA CAGAATCAGT CTCTGAAAGA 98460  
AAATCAGAAG AAGCCATTTG TGGGAAGTTG GGTTAAAGGC TTAATAAGCA GGGGTGCTTC 98520  
TTTTATGCCA CTCTGTGTTT CAGCTCATAA TAGAAACACT ATAAGTATT TACAACCTTC 98580  
AGTTAAAGGG GTAAATAATT TTGGTGGCTT TAAACTAAA GGTATAAACC AGAAGGCCAG 98640  
CCACGTATCC AAGAAAGCTC GTAAGAGTGC AAGTAAGCCT CCTCCCATCA GTAAGCCACC 98700  
AGCAGGCCCT CCATCGTCTA ATGGCACAGC TGCCACCCA CATGCTCATG CTGCTTCAGA 98760  
AGTTTTGGAA AAGTCTGGAA GCACCTCATG TGGAGCTCAA CTCAACCACA GTTCTTATGG 98820  
GAATGGTATT TCTTCAGCAA ACCATGAAGA CTTGGTGGAA GGTGAGATTC ATAACTTCG 98880  
TCTAAACTT CGTAAAAAGC TAAAGGCAGA AAAGAAGAAA TTAGCTGCTC TTATGTCTTC 98940  
CCCGCAAAGC AGAACAGTTC GAAGTGAAAA TCTAGAACAG GTGCCCCAGG ATGGGTCTCC 99000  
AAATGATTGT GAATCAATAG AGGACTTGT AAATGAGCTA CCATATCCAA TTGATATTGC 99060  
CAGTGAGTCT GCATGCACCA CTGTTCTGG TGTTCCTG TACAGTAGTC AACTCATGA 99120  
AGAAATTTTA GCGGAATTAT TGTCTCCTAC ACCTGTTTCA ACAGAGCTGT CAGAAAATGG 99180  
GGAAGGTGAC TTTAGGTATT TGGGAATGGG AGATAGTCAT ATCCCACCAC CAGTACCAAG 99240  
TGAATCAAT GATGTTTCCC AGAACACACA TCTGAGACAG GACCATAATT ATTGTAGCCC 99300  
CACCAAGAAA AATCCATGTG AAGTTCAGCC AGACTCTCTG ACAAATAATG CCTGCGTTAG 99360  
AACATTAAAC TTGGAGAGTC CGATGAAGAC TGATATTTTC GATGAGTTTT TTCTCTCTC 99420  
AGCATTAAAT GCTTTAGCAA ATGACACATT AGACCTACCT CATTCGATG AATATCTGTT 99480  
TGAGAATTAT TGAATTAATG CTTGTAACT TTTTTCATAT AATATTTATT ATTATTAGAA 99540  
GAACTTACAA TGTGTTCCAG TAGTGTAT ACACCTGGCT TGTGTAATTA CTTGTGTAAT 99600  
AACCATGAAC AAAATGCAAG GTTTAACCTT TGGTCTGCCC CATGAAGCAT GTAATCTTTC 99660  
TTACACATTA AAATCACTGA ATGTGTTCTC CTTTTGGTT TCATTTTGTT CTTGTGAGAG 99720  
TATGAGGATT TCAAAATGTT AAAGATGAAA AGTGCGTCT AGTTTCTGAC AGTTTGTACA 99780  
GTTGGATGCA TTACATTTT AGATTTGAAG TTTTGGTTAT GTTAGTGTTA TGAGTGATCT 99840  
TTGTGGTGGT TTTCTTCCCC TGGAACCTG TTGCTCGTGG CGCTTGCCC ACGGTGCCCC 99900  
AGTTCTTGTC CTGTGTCCAG ATATGCAGAC AAATGAAGGG TGAAGAAGAA GAAGAGGAGC 99960  
TTTATTTAGT GTTAGAACAG CTCAGAAGGA GACCCACAGT GAGCAGCTCC CCTGTGTCGG 100020  
CGGGCAGGTC GTCCCTCAAG TGTTCAAGCTC TCAGCAGAGA AAAGGCCCTG GAGAGGGTGA 100080  
CTCCTCTCAG CTCTCAGCAG AGAAGCAGCC CTGGAGAAGG TAGCTTCTGT TCGCAGGCAG 100140

FIG. 6.38

ATTGTCCAGA GGTCTGCTG CTCTCAGACG GGGCCCTGGA GAGGATAGCT TCTATCCATA 100200  
GGCAGGTTGT TCTGCCGTCT CTACAGGTCT CTGAAGCTCT TAGCAGAGAG GGTAGCTCCT 100260  
CCCTGTTGCT GGTCGTCCCA CCCTCTGCTC AGTTCTGGCT GAGCCTGGGG CATTTTACGG 100320  
GCCTCGGGGG AGGAAGTGCA TACTTACTGG CCTGAAAAAG GCACCAGTTC CCACTCCTAC 100380  
AGGTGGGACT GGCAGCCTGG CCCTCAGCCT TCAGGCCCTC CCTGTTTATG GCTTCCAGGC 100440  
TTACCCCTCT GCTTTGATCT GAGAGCTGGT GCCAATAGCA GGGAGAAGCC AAGCTGCAGA 100500  
GGCAAGCACT TCCGAGCCTG CAAAAGCAGG CCCCCAAAAG TGCAGGGATG CCTGAGTCTG 100560  
CACCCGCACC CAGGAGGGTG GAGATCTTGC CTGCTCCAAG GCTGCAGCCG GAATGATAGC 100620  
AGGCTGACTG GAGCACCTGC CACCATCATT AGTTCAAGAG TTTATGCAGA TTTAAGTTGT 100680  
ATACGGTATA TGAATGTGTG ACAGTTTTCC TTATGGTTGT GTGGCCTTCT GTAAGAGCCT 100740  
ACGCCTGTTT GTTACACCGG TAGAGTGCTG TGAATGTAA ACTTCCCTA TGCTACTTAT 100800  
CTCCTTTATC TCTCCATACA GAGGAGGGCA AGAAACCTTG TTAAGTGAAC TTTAGTAATG 100860  
TTAAGTGATC AATAAATCTA TAAATAATG ATAGCAGAAA AAAGTTACCT GTTTTTGTGA 100920  
TGATGTACAA ACTTTACATG TTATCACAAA TACCATCTTT CTTCCCAAGA CATTACTTTC 100980  
TGTAACCAAA GTGGGACACC ATCTAACAGT TCTGTTTTGG GAGAGAGTAA TAACCAGTGC 101040  
TTGTGAGGCT TGTAGATGT TGGTTGTGAT ATATGAGATA GATGTTATTT CATTAGACC 101100  
TCAACATTCC TGTGCGTGAG ATACTTTTAT CACATCTTAC AGATAAGGAG ACTGTACTCA 101160  
TTCAGTTGTG GAGCTGAGAT TGAGTAGAGT GGCTATTACA GCAGTTGAGT GCTGAGCTTA 101220  
TCAATATATG TTCCACTCCT CAGGCTTCAT TTAAGTAGG ATGCCCAAAC AGCACCCTG 101280  
CCGTAGAGAT TTGAGTTAAC AGCAGTACTT ACTGAGGTTT AAGGCTGGCA GCCAGTGTCC 101340  
TTGCAGTAAA ATTATTTGCT AGGGACTCAG TACTTCATAA TCTATTTGTC AGATTTACTC 101400  
CTAAGCTTCT GTGTTGTTTT ATTTTTTTTC TGACAAAAGT AGTGCATATT GTCAAGGAAA 101460  
AACTAGGAAA ATACCAAAAA AAAAGATTTT TGACCATGCA TTTAATACT TAGTGACTAC 101520  
AAACATTTTC CTATTTTATG CATATAGATT TAAATAAAC GTGAGATCCT ATTGTATCTG 101580  
TTTTAATGGA TAAACATTGT TTCAGTGTG TAAGATTCTG AGGTGATTTA TACTGTCTTG 101640  
CCATTGTAA TTGCAGCAGT TAGCCTTGTT GATAAATTTT TGCATGGATC CAAGTTTTGT 101700  
TTTCCAGGAG TGGAGTTGCT TGGTCAAAGG AAATGCACAT TTAAGGTTTT TTGGTGATTG 101760  
CATGACTGAC TTCCCTGGG CCTCGCCAAC ACTAGGTAGT AGTATTGGGA GGAAGGGGGG 101820  
AACCAATCCT GGGTGCTCCA AGATTACTAG TGAGCCTGAA CATTCTCTAT AACTATTGTC 101880  
CACTTGAGTT GTTGTGTTGT TTTTTTTTGT GTGGAGGCGG GGGTGGGTTT AAGAATTGCT 101940  
TATCCTTTCG TTGTACTAAT TATCTTTTCA ACAAATATT CTAGATTACT GCTAAGGACC 102000  
AAGCACTGTT ATCAGCCTGA GATAAGGCAG CACACTAGAA GGAAATCCTT GCTCCTTTTG 102060  
AGTTTGCTT CCAAACATGG AGATCAATAT ATAATGTTAG GTAGTAATAG GAGATACATG 102120  
CAGTTGATTG ATGTCATTTG TAGTAGTTAT GGTCAATAAA GTTGCCTTGA AACTGAATT 102180  
AGTATAAACT GAAATACTGT TCCTAGGGGA AATAGGTTCC TGCTAGCCTG TGGTCATGAG 102240  
ATTTTGTCA AACAATCACT ATATAACCTT TTCTGTTTCT GTTTAAAGAC ATGTTATTTG 102300  
ATCTATATGG TTGATTCTTT ACATTAACAT GGCCAACAGC ACTGTAACCTC AGCCTGAACG 102360  
AAGCTTATCT GACACATGGT GTTCTCCATA AGGCACATCA TAGCTTCTG TGCTTAGGAA 102420  
CACTAGACGG CACTTCAGCA CTGCACTTGA GGACGTTTTA AACAGTGAAA TCAACAAAAA 102480  
GCACAAAAAA ATGCAACAAT AGGCTGGGCA AGGTGGCTCA CGCCTGTAAT CCCATCACTT 102540  
AGGGAGGCCG AGGCGGGCGG ATCACGAGGT CAGGAGATCA AGACCATCCT GGCTAACACG 102600  
GTGAAACCCC GTCTCTACTA AAAATACAAA GAATTAGCCG GGCGAGGTGG CAGGCGCCTG 102660  
TAGTCCAGC TACTCGGGAG GCTGAGGCAA GAGAATGGTG TGAACCTGGG AGGCGGAGCT 102720  
TGAAGTGAGC CGAGATTGCG CCACTGCACT CCAGCCTGGG CGACAGAGCG AGACTGCGTC 102780

FIG. 6.39

TCAAAAAAAAA AAAAAAAGGA ACAATAACAA AGACACTAGT CCCCCAAAAA TACACTTGTT 102840  
TACAGTGTGA ACTGAAAGAG GAAGGTGGAG TATTGACTTG TTTGACCTCA GCTGGAAATG 102900  
TGCACGTCTT GTGACTCAAA TTTTCTCTG TTCTGTGCAT GCATGTCCAC GAATAACCAC 102960  
AAGAAGCACT GAAAGCATTG ATTTTATAGG TTACAAATTA ATTTTAGCAA GTAAATGAAT 103020  
TCACAAATAC GGAATCTGTG AGTAATGAGG ACTGATTCTT TTTTTTTTG GAGATGGAGT 103080  
TTCACCTTG TAGCCTAGG TGGAGTGCAA TGGCATGATC TCGGCTCACT GCAACCTCCG 103140  
CCTCCCGGGT TCAGCCTCCA CCTCCCGGGT TCAAGCGATT CTCCTGCCTC AGCCTCCCGA 103200  
ATAGCTGGGA TTACAGGCTT GCACCACCAT GCCCGGCTAA TTTTGTATT TTTAGTACAG 103260  
ACGGGGTTTC ACCATGTTGG CCAGGCTAGC CTCGAACTCC TGACCTCAGG CAATCCACCC 103320  
ACCTCAGCCT CTCAAAGTGC TGGGATTACA GCGTGAGCC ACCGCGCCCG GCCGAGGACT 103380  
GATTCTTATG TCAGATGGCA CTAAATGCTA TGGAGAAGAG GAGTGGATGA GAGGGAGAAG 103440  
TATTTTAGAC CAGGTAGACT TGGAAGGTTT CTTGGAGGTG GGTGATGTTT GAGAAGAGGC 103500  
TTCAATAAAG TTAGGGAGCT CGCCATGTGA TTGCAGGAAG AGCGTTCCAG GAGAACAAAA 103560  
GTCATGAAGA GTGAGTGCTA GGCATGTGTC TGGTCTGTTT GGGCTGCTAT AACAAAATAC 103620  
CTTAGACTGG GTAAAATGTA TAAATAATAG AAGTGTATTG CTTATAGTTC TAGAAGCTGG 103680  
GAAGTCCAAG ATCAAGGTAT CAGCACATTC TGGTGAAAGC TGCTCTGCTT CATGGCTGGT 103740  
TCTCTCACTG TCCTCACATG GCATAAGAGG GGCACAGAGC CCTCAACCGT CTCTCCAGTG 103800  
GCCCCATCTC TTAGTACTGT TGGATTGGGG ATTTAGACTT CACTAATTTT GGGGGGACAC 103860  
AAACATTGAG ACCACAGCAG CATGACTGAG GATAAGCAAG AGGCCAGTGT GGTGAGCAG 103920  
AGTGATCAGT GAAGGAGAGT TAGGACATGA GTAAAGAGGC TAGCAGACAC CAGATCTCAT 103980  
ATGGCTTTGT AGGCCATAGT GAGGACTTTG TTTAAGCTGA GAATAATAGA TAACCTCAGG 104040  
AAAGTTTCAG GCAAGAGGGT AACATGATCT GATCTGGGT TTTAAAGGAT CACTGAAGTG 104100  
GGGAGACTGT CTACAGATGG TCTGAATAGG AGTCCTAGTC TATTACAATC TCCTGGAGT 104160  
TTAGGGTGGT AACTGGAGGT GTTCAAGAGT AGTTGGATTA CTGTTGGATT TCAAAAGTAG 104220  
AGCCAACAG ATATGTGCAT TGGCTGTGAG GTAGAAGAGG AGTCAAAATG AACTCCAGGT 104280  
TTTATTGACT GAGCAATTGT GCCATTTCTT GAGATGGGTC AGATTTGGGA AGGAAAGAAT 104340  
TTAAAGGGGA TAAGATAATC CCATTAGGAG TGTGTTAAGT GTGAGATTCC TATTAGACTT 104400  
TCGAGTGGAG ATGATTTAAT AGGAAGATAG ATCTGCAACA CTGGAGCTCA GCGGAGAGGG 104460  
ACACCCTGGA GATAGCCGTT TGGGAATTAG GAATGTGTGG ATCATGTTAT AGGATGGGGT 104520  
CATTTAGGGA CTTAAAACAG CTCTGAAGAA CAAAATGGT GCCTTGATCT TGGACTTCCT 104580  
GGTTTATAGA ACTGTGAGCA ATATATATAT ATTTTTC AAGACAGAGTC TTGCTCCGTC 104640  
ATCCAGGCTG GAGTGCAGTC GCACCATCTC GGCTCACTGC AACCTCCACT TCCTGGTTCA 104700  
AGCAATTCTG GTGCCTAAGC CTCCCAAGTG GTTGGGACTA TAGGTGTATG ACACCATGCC 104760  
CGACTAATTT TTGTATTTT TTGTAGAGAC AGGGTTTTGC CATGTTGGCC AGGCTGGTCT 104820  
CAAACCTCTG ACCTCAAGTG ATCTGCCTGC CTTGGCCTCC CAAAGTGCTT GGATTATAGG 104880  
CGTGAGCCAC CATGCCCAGA CTAAATTTCT AACATTTATA AATTATCCAG TCTAAGATAT 104940  
TTTGTGATAG CAGCCCAAGC AGACCAAGGC AAAGGCCAAG CACACTTGCT CTCCTGACT 105000  
TTTGCTCTC CTGGAATGTT CTTCTTTAG TCACATGGTT GCCTGCCTAG CTTCAATCAA 105060  
TAGGAGTGTG GTGCCCTGAA AATACAAGGA AGAATGCTTT TCTTTTTTTT AAAAGGAAGG 105120  
GATGATTATC TGTCAGATGC TGCTGAAAAA GAGTAATAGA GTAATTGGCC ACTGGCTCTG 105180  
GCAATAGGGA AGTTAGCTCT GCTAACTCCA CATGAACAGT TTCACATGAA CAAGTGTGAG 105240  
TGGGCTCAAG AGAAGGGATG GTGAGAAAGT GGAGCTATGG ACTCACTCTT GAAACATTTT 105300  
CTGGTGCTC GTAGGGCAAT GTGAGGTCAA GGTTTTTGTT ACTGTTCTGA AGATGGGAGA 105360  
GGCTGACACA TGGATGTTGT AGGTGAGAGA AGGGGCGCTT GCGGGGGCAA ACTTCTCCAG 105420

FIG. 6.40

GGATGGGATT CCAGTGTCTA AGAGGAGGCG GTGTGACCCT AAGAGCTAGA AAAATTATTT 105480  
TATTAATAGG AAAGACAAAG TACTTAGGCT CAGATGCTAA GAGATTTGCT GATAAAAGAA 105540  
TGAGAACGGT CTCTTCTGAT TATTTTCTTG GGGAAATAAA TAGATCATCA GCTGAGGGTG 105600  
TGAGGGGAGA AGGAGTTGAA CATGGAGGAA GACAGGTGTG AAATATTGGT CTCAGAATGG 105660  
AGAGCGAATT GAATAGGGAC ATGCAGTGGG CTTGCTAAGC TGTGCGGAGA GCCCGTGGGA 105720  
AGTTTATGGT CATCAATTTA ATGGCGACCA GCCAAGATGG TGGTTTATTT TTCTCCAGTT 105780  
GTATTTAACT GCTCAGGTGC AGGACAGAGA GACTAAGTGT GAAGTTAATT TCAGCCAACG 105840  
TAGAGGAATT GTCAGGCAGA TGGGACAAGG AGATAGAGGA GAAAAGGAAT AAGGCTTCCT 105900  
GCAAGGGTAA TGATTGTAGG GATGGATAAG TAAGGAACAC AGGAAGTGGC TGTCTGCTGA 105960  
GTGGTGCCAG AGCTCAGTGG GTCAGAGCAA GGTTCAAAGA ATGGCAGAGA GGCACCTGTG 106020  
GAGGAAGTAA GCTGGCTAGA AAGTAGTGTG CTTGAAATTA AGCTTCTGGA GATAGCAAGG 106080  
TTACAGGTGA TGACAAAGTC TGAGTATGAC AAGGAACTG CAGGGCCAGA GTTGGCAAGA 106140  
ATTCATGAAA AATGAGGAGA AAGAGGCACC AAGAGGCTGG GATAGCACAT GGATTGTCTC 106200  
TGTGTGAGGC AAAGTCATCT AAATGGCAGC AGTGGCCCTA GCAGAAAGAA ATATACAGTG 106260  
AGCCGGAGCA AAAATCCTCA AGGACAGGCA GAACGCCATG AAAACGGCAG ATGACAGCCA 106320  
AAGGAGCAGG GGCAGGGGGCT CAGTCCAAAG TGTTTCAGAG TCACTGGAGG GTTGAGTGGG 106380  
AAGGGGAGGG AGTGGCTGAA ATGGCAACAA GGAAGAACCT CTCTCATCTC CAGGCCCAAA 106440  
AGTATGTGGA ATGCGGGAGA TAAGACAGCC ACCACTGGCC AGGGCTGTAA AGGGACATTC 106500  
AGCGAATATT CAGGTTCCAT TTAGCACGAC AGCAGGGAAG GGAAGTGTGG CAGAAAAAAA 106560  
CTGGGGCAGT GGGATTAAAG ACAGACCACA CATTCCAAAA GGCACCGTGG GAGGGTCAGG 106620  
GGCGCAGGTT AGGTCTAGGC TTCAGTGTCC TGGGAGACTC AGTCTTCACA GGGTGACAGC 106680  
GATCAAGAGT GCAGCTTAGG CTGGGTGCAG TGGCTCATGC CTGTAGTCCC AGCACTTTGG 106740  
GAGGCCGAGA CGGGAGGATT GCTTGAAGCC AGGAGTTTGA GACCAGTCTG ACCAACATGG 106800  
CAAAACCCCA TCTCTACTAA AAATACAAAA ATCAACTGGG CATGGTGGCG TGTGCCTGTA 106860  
GTCCAGCTA CTTGAGAGGC TGAGGCAAGA GAATCACTTG AACCTGGGAA GCAGAGGTTG 106920  
CAGTGAGCTG AGATCGTGCC ACTGCACTCC AACCTGGGCA ACAGAGTGAG ACCCTGTCTC 106980  
AAAAACAACA ACAACAAAAA AGAAAAGAGT ACAACTTATG AAGGGGTCTC CTGGGGAGAG 107040  
GGTTTTTGGG ATTCTCCTGC CTCTCAAAGT GCTGGGATTA TGGGCGTGAG CCACCACACC 107100  
CAGCCGAGGG AGGCTGAGTT CTAATTGTTG TATCTCTCTT GGGATTGGCC TCCTGGGCAG 107160  
TTTAAAAGAC AAGGCAAGGA ATCTTTTGGG GAAAGAGACT GGGGGCAAGG TGTGTCTGAA 107220  
CAAGAAGTGT GAGAAGCTCT GTGGGCTCCC TTCAGACTTC CAGTCGTTGA ATTGGGATCT 107280  
CATTTATATC AGCTCTAGGT GTAACGATAT TAAATCTTCT CTGTCATTTG GCAATTTTGG 107340  
TTTATGCTTG ATCATCATTT TTAATGTTTC GACATGTAGA AGTTTAACAT TATTTTACAT 107400  
TCTTTTCCTT CTGGCATCAT GTTTTAGCAA GATTGTTTCC ACCAAAAGAA TATATATATC 107460  
TTCTAATGAA ACTACGTTTC TTTTTTTTTT TTCCTTTGCT TTCTCTTTTG GTATATGAAT 107520  
CTTTGATTAT TTGTAATGTA TTTTGATGTG TAACACTGAA GTTTCTATTT TGTACTATTT 107580  
TTTTCCCAA ACAGTAAACT TATTGTTCAA ATACTTATTG AACAACTTC ACTATTCTTT 107640  
AACCATTTAG AATACGCCAT TCACATATCT TTCATACTAC ATTTAATAAC ATTTTTTAAT 107700  
TAAAAAATAT TCTACTGATT TGTTTATTTT GAGACCAGGT TATGAACTG GCTAATTTTT 107760  
GTATTTTTGT TAAATACCGA AATTCAGTGT GTTGCCAAGG CTGGTCTCGA ACTCCTGGGC 107820  
TCAAGCAATC TGCCACCTT GCGTCTCAA AGTGCTGGGA TTACAGGTGT GAGCCGCTAC 107880  
ACCCGGCCAC ACCCGGCCAA CACATATTAT TTGTTATTAC ATTTAATTCC CACAGTACAT 107940  
TGAAATTATC AGGGAAAAAGT TTTCAGTGAA ACATTATTGA ACGCCACATT AAAAGTGTA 108000  
ATTACAAAGA TTTAATGCCA ATTTTTCAGA AGAAAAAGA CCAGGAGGAA GGTCTATGAA 108060

FIG. 6.41

GTTTTAGCCA GTCTCTCATC CACCTACCAT TTCACGATCA TGCACGTGT AAGTCAGGAA 108120  
AAGAGTAAGA AAAGTGAAAG ATACAATTGA TTAGAGAGTT TTGCTGGATA CTATAGATGA 108180  
AAAGAACACA AAATGGAACA GCCTCTTCAA GCTTAGAGTC AACGGCTGTA GTCCCAAAGA 108240  
CTGTAGTCAG AGGCGGTAGG GCCAAAAGAC ATGACTTATG GCATTGGAGG AAGAGGATGC 108300  
TTTGGGAGTT CATGGTAGAA GAGGCGGAAA AAATCTGGTG GATTAAAGAA AGCATCCCAA 108360  
AGTGACATTA AACTAATGAC TAAATTCTGA GCTGTTTTCA GGGGCAAAGC CTGTTTGGGC 108420  
ACCCCTGCCA CACTTAAAGA GTCACCTAGG TATGGTTCGT GGGCTCTGAA CAGGCCTGCT 108480  
CAGTGAACAT ATTTGTGACT GTTCTCCGG CCCTTTTAGC TGTATTGAGT AAAATTTAA 108540  
GAGACCATTG TTTTGGCCTA AGCTCCTGCC CTAGGCCCAA AGAACAGACC AAACCTGAAT 108600  
GGCTTCACTT GTCCTAGGTG CTGTGTACTC AAAGTGAAGT TTGAAACAGG TCGGTTTTTC 108660  
AAAAAAGCA AAAGATTCAC AGCAACCAAT TAGAAGAGGC CCGTCAACC TGAGCCAGCA 108720  
TGATGAGGCT CTTCTGCTTT AATCCTACAA GGAAAGAAAC TTTGAAATGA CCAATCTGCT 108780  
TTCATTCTTG GTTCTGCTT TCTTTGGTCT ATTTCTGCCT GTAAACCTA TCTCCTCTGC 108840  
TCAGCTCATT GAAGTACCCT TCTATTTATA GATGGGATGC TGCCCGACTC ATGTATCGCT 108900  
AGTAAAAGCC AATTAAATTA TTACACTCGA TTTGTTGGAA TTTTGCTATT TTGACAGCTT 108960  
TTCAAAAACA CCAGTAGGTT CACATCCCTA ATCCCCAGC CAGTGTCCC TCAAGGAACC 109020  
ATGGAAGAAG CAAAGGTGGC TGAAAGGCGC CTCAGGATGC TTCTAAGCAC GGCACATCCA 109080  
TGAAAGGCA CTTACTAATA TTTGCAGGAT AGCAAAGCAC TGCAGTGACG ATAAATCTAG 109140  
TATTGGAGAA GTTCAAAATA ATCAGTAGAT TAACACAGAA GCCAGAGCTT ATAGGGAGAA 109200  
AAGGAACCCT ATGAAATACT TCAAATCCGA AAACGAACAT GCATTTCTG TTAGTTAGT 109260  
GCAGGTACGT AAAAGCTTGG TAAAGTACCC TTCTTGCCAG CTTTCTCTT CTTACAAGCC 109320  
TTTTCACTGG GCTGGGAGGC TGATATTATC TAAATATGCT GAGGAGGTT CAGTATCTCC 109380  
ACAACACACC TCAGAGTGAA TGCTCCCTC GGCCTTAAGG CAATATAAAC CAGCCCTGTT 109440  
TAGCAGGATA GCAAATGTT TGCGGTTGTA AACTGGTGT CCATTGGCTG TGGCGCTTGT 109500  
GGTGTAAGA ATCCCTGTGC TTGGTAATTA ATAGAGAAAT TCTATATTT AAACCTCAGT 109560  
TGTATATTGG CTCTATCCA TGGCAGATT TCACGTATGT GTTATTTTT TATTATTCA 109620  
GAGCCGGAGT CTCGCTTTGT CGCCAGGCT GGAGTGCAGT GCGCGATCT TGGCTCATTG 109680  
CAGCCTCTGC CTCTGGGCT CAAGCAATTC TTCTGCCTCA GCCTCCCTAG TAGCTGGGAC 109740  
TACAGGTGCA TGCCACCACG CCCGGCTAAT TTTTGTATT TTAGTAGAGA TGGGGTTTCA 109800  
CCGTGTTGCT CAGGCTGGTC TTGAATTTCT GAGCTCAGGC AATCCGCCCC CCTCGGCCTC 109860  
CCAAAGTGCT GGGATTATAG GTGTGAGCCA TCATGCTCGG CCCTATGTGA TATTATTAC 109920  
AATGAATTCC AATGATCAGA CCTATACTCA AGTATAAGTG AATATATCAT TCAATGAAGT 109980  
ATAAATGATC ATTATGTTCA TATTCACACA TACAATAATG TACTCAAGTT TATTGCTAAG 110040  
GTAATTCAGA ATCTCCTTAT TTTGAAGTGT GCATTTGATA TACCTGTTT GGAATAACTA 110100  
GTTCTTATC TTTGACAGAA AATAATTTT TGTGTTTGT TTTACTAAAA AAGCATGGTG 110160  
AAAAATGGCT CCATTTCTAA GAGAGGTAAC TAAATATCG CAATTTGCTG GGTGTCATTA 110220  
AAGTAACTCA CAAGGGAAAA AATGCAAATT GGTATCTGCT GATGGAGTAA ATCTCCGCAG 110280  
AAGTGATGAC CCTGAAAGGA TCAATATATT AAAGCCCTC CCAGCTGGTC ATTCCAGATT 110340  
GCAACAATAA AGCATTAAGT GTTAAACCT CAAGGCAGCT TTTTTTTTT TTTTGTCT 110400  
CAAGTCCTTT ATTATTAATT TTATAGACCT ACTTAATTAC TAAGCCAAAA AAAATCAAAC 110460  
TTGTTTCTCT TTGTGACTTG TCAATAGTAT TAACTATTC TGGTTTTTA TTTTGTGTT 110520  
ACCTTAAAGT CTCCAGTTTA GTAATTTTTC TGTACCTAAA CACTTCGGAT TTGACATGCT 110580  
TTGTGGCCTT TATCAGTAGT TAGAATGTAA ATCCAATAA TAAAGTAAAA GCCAGGTCTT 110640  
CAAAACCTGG GGGCCAAGAA CTCTGTTTGA GAGGGCCTGT GACTCTCTG GACACTGGAC 110700

FIG. 6.42

AAAATCTCAT CTCTAAATAT GGATATTTTA GGGAGAGGGT CTTTAGGCTG TCATTTGGAT 110760  
TTTCACAGGG CTCCATGTAT CCATAAGGTA GTCTCTTGGG AAGTTTGACT TCAATAAATG 110820  
AAGTTTAACT TAAACCTAAA ATGAAATTTA ACTGAAAAAC AAAATCCAAT GAAAGATGCT 110880  
TTCTTATGCA AAAACAAACA AACAAAAAAA AACAAAAAAA ACCCCAAAAA ACCCAAAGCC 110940  
AAAGATTGTT TCTGAAATTA GGTTCAGGT TCCAGAGCAA CTCCATGGTG GGAATCAGC 111000  
CACATGTAAA GTAAGCTAAG AGTTTGGACA ATTTGTAATA TTTATTCCTA GGTTTCTTTA 111060  
AGACCCTTTC AGATTTTGAA TTCCTATTAG TAGCATCAGC CAGGTTCTAA ATGTAGGCAT 111120  
CACCATAGAC ACTTCCCCAC TGCTGCAGTC CCCAACACTT GCCCAATTTT CCCTTGAATT 111180  
GCACCCATGC TGCCTTCTCC AGGCCTATTT GAACCCAGAA CCTCGTTGTG CCTCGTTTGA 111240  
AATATAATTT CCTCCTAACT AGTCTCTGAT CTAATTTTTC CCTACATTG CTGCCACACT 111300  
AATCACCTAA AATAGATTTT ATTCTACCCT GAAACAGAAA TCTCTAATAA GTTACTCCCT 111360  
TCCCTTACGG GGTAAGTTA GCCACATCCT AGGTATTCAA GGACCTTCCA GGAGCTAAGA 111420  
ACATTTCCCC TGCACCTTCT TGAAGTACAC TTGTCCTATG TACTGGTTAT GTTCATTTCT 111480  
TACCCTCGCT CTCGTTTTGT CTGGAATTTT CCTTGGCCTT AAATGCCTCT CACCTGCCTG 111540  
CCCACATCTC TCAGGGTTGT TTCAAATCCT CAATGAAGGC TCACAGCCCC AGTCTATGTT 111600  
GGCCACTTAC TTCGTGGCCT GGAACATTTT TTCTTTGGCT GACTTGCTGA CACTCCATCA 111660  
GATGCATTTT TATCTGGTTG TCCATCTGTG AACCATACCC TGAGAAGGCA GAGAGTGCCT 111720  
CTGCACTGAA CATGTGCTAG GGGACAGGTC TGTGCTAGAG GGGCAAGCAC TGGAATGAA 111780  
GAACTGGTCC CTAATCCCAA GGAGTTCATA TCTCAGTGGA GGTGACAAGC AACTCACTGT 111840  
TTCCGGGGGT TGTGGTGAAT GCTGGGAGAA GGGGTGTCTA TATTAGATCG AAGCAGCATC 111900  
AGGGGAGGTT CCCTGAGAAG GTGATGCCTC AGCGGATGTC TCCAGCTAA GTGGGGTGGA 111960  
GGTGGAGAAG GGCAGAGCAG GGAGAGGATC TAGGTGGGGC GTGTAAGTCT GCATGGGTAA 112020  
CTCAGGGAAC CCTTGGTAAC TGCATGTAAC TGTGTGAAGC TTTCATGAAG GAACATGGTA 112080  
GGAGACTAGG GTATGGACTA TAGAAGCCCT TTTGCTAAGC TCAAGAATTT GAGGCCGGA 112140  
GCGGTGGCTC ACGCCTGAAA TCCCAGCACT TTGGGAGGCC AAGGCGGGCG GATCAGGAG 112200  
TCAGGAGATC GAGACCATCC TGGCTAACAT GGTGAAACCC CGTCTCTACT AAAAAAAG 112260  
TACAAAAAT TAGCGGGGCG TGGTGGCGGG CGCCCGTAGT CCCAGCTACT CAGGGAGCTG 112320  
AGGCAGGAGA ATGGCATGAA CCCGGGAGGC GGAGCTTGCA GTGGGCGGAG ACTGTGCCAC 112380  
TGCACTCCAG CCTGGGCAAC AGTGCAAGAC TCCATCTGAA AACACAACA ACAACAAAA 112440  
ATTTGAAGTG TATCTTGAAG GAAATCCCTT GGAGCCTAAA AATGATCATT GATAACAGAA 112500  
AATGATCTCT GCTCTGCCT AGGGTAATAT ATTCAGCTTC AAAGTGGAAG GGCATGTTTT 112560  
CCAAGGGCAT GTTTTCTAAG TCCCTGTAAT TGTAAGTATA GCAATATAT GCCCTGCATC 112620  
TTGAAATGTA AGACTAGGTT TGAACAGTAT ATAAATTATC TTATGATCTA ATTTCCCTC 112680  
ATTTTGTGGT TTCTACTATA AGCTACCCAG AAGTGTAGAC AGGACGTTTG GAATTTGATG 112740  
GGCATCGGAA AGATTCTAC CTAAGAACAT TTTTTTTTTT TTTTTTTTTT CTGAGAAGGA 112800  
GCCTTGCTCT GTCACCCAGG CTGGAGTGCA GTGGCACGAT CTCAGCTTAC TGCAACCTCC 112860  
ACCTCTCAGG TTCAAGTGAT TCTCCTGCCT CAGCCTCCTG AGTAGCTGGG ACTACAGGTG 112920  
TGCACCATCA TGCCTAGTTA ATTTTATAT TTTTAATAAA GGCAGGATTT CACTATGTTA 112980  
GCCAGGCTGG TCTTGAATC CTGACCCCAT GATCTGCCCA CCTTGGCCTC CCAAAGTGCT 113040  
GGGATTACAG GTGTGAGCCA CTGCGCCCGG CCTCTAAGAA AATTTTGTAG AGCTACTTGT 113100  
TCTGTTGCCT GGAATTCCAC CGTAAGTACG ACGTTGTGTC TCCTTCTCCA GGGCTACTAA 113160  
CTAAACAACA GAGGGTATTG TGTTATCGAC AATTATTTGA TTGATAACTA TCAGCAAACA 113220  
TTTGCCAAGG CATTCCTTTA AAGATAGCCT AGTGACTCTA TTAATACTC CTTCTTCCAG 113280  
GCTTCTAAGT TCTGTTGGAG GTAAGTAGAT CCCAGAGATA AAGCACCTAC CATAGGACCT 113340

FIG. 6.43

GAATCTTGGT AGAAATAAAT TATATCATCA TGTTATCATA TTATCATGTG TTTTCTATC 113400  
TTTAAAGTCT TATGTGAATA TTCTGCTTGA AAAATATGTG TCCTCTGTGA GACCAGAGTT 113460  
GAAAATATGT TATTCAAGAA CTTGTAACAG GAACCCGCAC AATTTCTGCT GGAGTTTAAT 113520  
TTCAGGGTTA ATTCTGTCAG CAATCTAAGG TAAACATTAA CATTTTCCC TAGATTCAAG 113580  
TCCGTTGTCC AAAAGCTGTA ACAGAACTTA ACTGAATAAA TAGTTTCTTA AGATGGTAAG 113640  
CTTCCATATG CTTATAATGA CTCCTCTACA CGTTTTTCATC TGGAAGGCTG CTCATGCTTT 113700  
TGGAAGCAAA GAAGACAATC TTAATAACT ACATTTGCTT TTTGGTGGTG CCAGATTTT 113760  
CTGAGAAACA CCAATGGAAT TTATAAATC ACCAGTCAAT GGGCAATTGA GTTGCTGTTT 113820  
TGCTATTACC ACTGCCGTTT GTGAGCATTG TTGGGAAGGT GTCTTGAAGC ACACGTGCAA 113880  
GTTTCCCTTG GATAAGTAGT AGGAATAGAA TTGCCAAACC ATGGCTTCCA GTGCAGACAC 113940  
AGTCTCTCCC TTGGGCCAG CCACTAGGCA CCACACATTA AGAGGATATT GTCTGTCCAT 114000  
GTCCTAGAAA CGTTGTAGCA TCATGCTCCT ATTCGATTAA AAATCTCATT ATTAATGA 114060  
ACCATCGGGT AAATGTTGTC TCGGGAAAAG AAGCACTGAC CGTCCCTGGG TGGGCTCGAA 114120  
CCACCAACCT TTCGGTTAAC AGCCGAACGC GCTAACCGAT TGCGCCACAG AGACCCAGTT 114180  
ACTCAGGCCG CGCTGCGGTG TGTACAGATT TCCGCGGCGC CGGCAGCCGC TCTAGCCACC 114240  
CTGGGCGTCG CCACCCAGG CGTTGCCACC CCAGGCACGG GCTGAGAAGT CGCGGGGCGC 114300  
GCCGAGGAGG CAGCGGAAGC GGCCGAGGTG CCCAGCGGCC GCCGCGGGG GAGAGGCTGT 114360  
GCCCCGGCGC GCGGGAGGGG GCGGGCGAGG CCGCGTGA CTGGGCTTCT CTGGGGACGA 114420  
AGCGCGCCCC TCGTGCGGC AGCGGCCAGT GGTCCGCACT CGGCCCGAC TCGGGGTAGG 114480  
AAAGATCCTC TCAGCAATGG CTGCGCGCCA TCGTGCTCT GCGGCGGGGA CCGTGCCGGC 114540  
CGGGCGCGCC ACCAGTAACC AGGGACCCAG GGGAGAACC GTCCAAGGGGA ATAGGTGCGA 114600  
CGGAGAGAAT ACGACACGCT TGGAGGGAAG AACCACGTGC TGTACAGGT TAAAGGATGG 114660  
AGAGTCACGT GCGCTTAGGT CCCAACTTA AGGGACCTAA CCCTTTTCT GGGTTGCCG 114720  
TATTGCCCT TCTCCTAGA CAGTTTTCA TCTCATCACC TCTACCCCG TAAATGCAA 114780  
CGAACATAGA TAGGCTGTGT ATCAATGTAG ACTGTATGTA TATCTGTGCT TCGTACATAA 114840  
AAAGAATATG ATTTTGGCA CCTTCTAAGA ACCAATTG ACCTTATTT GAGGCATATG 114900  
GCCTCTGTTG AGATTGCATA GTTTAGGGGA CATCAAAAA GCCTTATAGA GGGACTGGCA 114960  
ATTAAGATAG CCTTTCAGT TGAAATGGCC ATTGAAGGCT TCTCCCTTC CCTGACTTCT 115020  
GAATTTTTT TTTTTTTTT TTTTTTTTT TTGAGATGG AGTCTTGCCC TGTGCTGGA 115080  
GTGCAATGGC GCGATCTCGG CTCACTGCAA CCTCCGCTC CCGGGTTCAA GCGATTCTCTG 115140  
CCTCAGCCTC CCGAGTAGCT GGAATACAG GCGCCTGCCA CCAAGCCAG CTAATTTTG 115200  
TATTTTAGT AGAGGCGGGG TTTCGCCATG CTGGCCAGGC TGGTCTGGTA CTCCTGACCT 115260  
CGTGATCCGC CCGCCTCCGC CTCCCAAAGT GCTGGGATGA CATTACAGGC GTGAGCCACC 115320  
GTGCCCCGCC AATTTTTTTA GGCGCACTGT TCAGTGGCAC TAAGTACATT CACATTGTTA 115380  
TGCAACTATC ACCGCCATCC ATTTCCAGAA CCTTTTCATC TTCCGAAACA GAAGCTCCCT 115440  
ACCCATTACA CGGTAACCTA CGATTCCCCT CCTCTAGTCG GAACAATCAC CATTCTACTT 115500  
TCTGTCCCTT TGAATTTGAC TACTCTAGA GACCTCATGT AAATGGAGTC ATACGGTGTT 115560  
TGCTGTGGC TGGCTTATT CACTTACCAT ATGTCTTCAA GGTCCATCCA CGTTGTAGCC 115620  
TGTGTCAGGA TTTCCTTCCT GGATAAGGCT GAATAAGCTG CACTGTATGC AGGTATCGCA 115680  
TTTTGCTTTT CCATTCATCT CTCCGTGAAC ATTAGGGTTG CTTCCACCTG CAGCTATGAA 115740  
CATGGGTCTA CAAATAACTG ATTCCTGCT TTCAATCTT TTGGGAATAT ACCCAGAGAT 115800  
GGAGTAGCTG GATCACATGG TTTGCTATTG GCTGTACCAT TTTACATTCG CACCAACAGT 115860  
GTACAAGAGT CCCTATTTCT CCTCATCTAT TTTTTTTT AATAATGGGC ATCCTAATGG 115920  
GTATGAAGTA TCATCTCATT GTGGTTTTGC TCTGCATTTC TCTAACGATT AGTGGTGTG 115980

FIG. 6.44

GGCATCTTTT CCAGACACCA CCAATCTGAA TTCTATGGCC CTTCGTTTAC TCACTTCCTC 116040  
CCAGCAAGAG CCATTTCTGC TTCAGCAAGG AGGAAGCTGC GACTGATAGA GGGAAAGGGC 116100  
CCAGGGGGCT TGCAGAGTGG GGCCTGTGCC ATGCAAGGAG AGGAGAAGAA GGTGGATCTT 116160  
TGAGTAGGAC TATCTGGAGA TCCTGCTTTC ACAAGGTCCT TGCTTGTGTG CTGGGCAGCT 116220  
TTTGGAGCTA GTTATCTTTA TTTTAGCCCT TGAGGGATAT TTAGGCATGT GGTGCTTGTG 116280  
AGCAGCCAAT CCATGAAGAA GGAAGTATG GTCTCCACCT TGGAAATATT GGAAGAGATA 116340  
ATGCCGTCCA AATTGCAGTT TTAGAAGTTA ACTTAAAATT ATGCTATTTT AATGGAATTT 116400  
TGGGTGCATT TCCATTTTCT TCTTAAGAAT TGCTGGAATT TCTTAAGTGT TTAGGTGATG 116460  
ATCTCTTTT GTGATTCCTT TTTTAAAAA CAACAACAAA ATCTTTCAAA TACATAAGAA 116520  
ATAGGCCGGG CACGGTGGCG TAATCCCACC ACTTTGGGAG GCCGAGGAGG GCGGATCATG 116580  
AGGTCAGGAG ATCAAGACCA TCCCGGCTAA CACGGTGAAA CCCCCTCTCT ACTAAAAAAT 116640  
ACAAAAAATT AGCCGGGCGT GGTGGCGGGC GCCTGTAGTC CCAGCTACTC GGGAGGCTGA 116700  
GGCAGGAGAA TGGCATGAAC CCGGGAGGCG AAGCTTGCAG TGAGCCTAGA TCGCACCACCT 116760  
GTACTTTAGC CTGGGCGATG GAGCAAGACT GTCTCAAAAA AAAAAAAAAAG AAAAAAAAAAG 116820  
AAAGAAATAG ACCTTTATTT TTCTGTAAT CCACAAAATT TCTATTTTGA TTCCTATTA 116880  
TTTTGCTATT GTCAACACAG TCTCAGTCAA TTCAAGATCC TGTTTGTGCC TTTCCCTGGA 116940  
GTCATTTCCA AGTGCTAAGG CTTTGGTCCA TGAGTCGCAT GTGCACACTC ATGGCTGTAG 117000  
AGGGAGTTTT GCTCCCGGTG AAGGTCTTGG TGGCTCTTCT ATACCTTGAT TGAGGGAAAG 117060  
GAATCTTATG TGAAGTTAGC TTTGTTGTAT CAGATATTCC ATAAAGCCAT TTCTGGGACA 117120  
GTCCCTCTG TTTATCGGAC CACAAGCTTC TCTGTCTCA TCAAGCCAC CTTTATACTT 117180  
CATTTCTCCA GACTTCATGT CCAGACTGTG GGATGAACAA GTGGTTATAA GGTTTTAGAG 117240  
GCTCCTGTAG GACTAGATGG AAGGCAAAAA AAGGAAATAA CCTTTAAGCA TGCTCTCGAT 117300  
TCCTTAAATC CCATCTGAAA GTCTTAAGGA TGTCTTCTCA GTCATACTTA TTTGACAATA 117360  
TTACCTAATT TTCTCCATTA GCCCAAGCTC AGGGGTCTTT CTTCTTCCAT ATTCACATGG 117420  
GTGCAATGGT TTTCTGAAAG GAAAACAGCA TTAGTAGGGC AGTAACATTT AATTAATCAC 117480  
AGGTACTTAT CAAACTACAA AACAGGCATT CCAGGAACTG GGTGTTTCTG TTTGTAAAAT 117540  
TACACTCTCG TGTACATGCT CCCACTAAAA TGTAAGTTCC CTGAGGATGG AGGTTTTGGT 117600  
CTCTTTGCTC TGTGCTGTAA CCCCAACACT GCAGCAGGGC CTGGCACATA GCAGGCATGC 117660  
AGGGACTATG CACTGAATCA ATGAGGAAAT GAAAACCAGG ACCATGAAGT AAATGGGACA 117720  
AAATAAAATG TGATAGAAAA TCTAAATTCC TAATACATAA GGAGCACTTA TCAATTGATA 117780  
TTTACAAAAT CTTTTTACAA TTCAATTAAA GACAACATAA AACAAATAAG AATGGGGACA 117840  
GGAACAGAAA ATTCCCCCAA AGAAAAAAAT ATATATACAT GGTACAGCCA TTGTGGAAAG 117900  
CAGTATGGAG TTCTCAAAAA TATTAAAATA GAACTATCAT ATAATCCAGC AATCCCATCC 117960  
CTGGGTATAT ATCTAAAGGA AATGAAATCA GTACCCCAAA GAGGTGTCTG CACTCCCATG 118020  
TTTATTGCAG CATTAGTTAC AACAGCCAAG ATATGGAATC AACCCATCAG CAGATGAAAG 118080  
GATAAAGGAC ATGTGATACA TATACACAAT GGAGTAGTAT TCAGCCTTAA AAAAGAAGAA 118140  
AATCCTGTCA TTTGCAACAA CATGGATGAG CCTAGAGAAC ATACTAAATG AAATAAGCCA 118200  
GGCATAGAAA GACAAATGCT GCATAGTCTC ACTTAGGTGT GGAATCTAAA AAAGTCAAAT 118260  
TAAAAAATAA TGTCAGCAG AGAATAGAAT GGTAGTTGCC AGGGACTCTG GGAAGTAGCA 118320  
GGGGTGGGGG TGGAGGGGAG GGGATGGGCA GAAGTTGGTC AAAAGGTACA AAGTTTCAGG 118380  
TAGACAGGTG TAAGTTCTGG GGATCTATTG TACAGCGTGG TGACTGTAGT TAATACTGTA 118440  
TTGTGTACTT AAAAATTGCT CACCAAAAAT GTTCTACCA AAAAAATGAT GTTTGGATAT 118500  
GTAAACAGT TTGATTTAAT CATTTTGACG TGTGTGTGTG TGTGTGTGTG TGTGTGTGTG 118560  
TGTATACATC AAAACATCAC ATTATATACC ATATACAATT AATATATACA ATTTTGTCA 118620

FIG. 6.45



AAGAAAAAAT GCACATGACC AATATGATAA AAGTTTAGTC TCACTAGTAA TAAAAATCAA 118680  
AATTAATGA AATAAAATT TCTTCCCCA AATCGCAAAA GAGAAAGAAA GGTAATACTA 118740  
AAACACAGTC ACGGTGTAGT GAGAGGGCTG CTCTCACACA GGA CTGATGA GAATAAAATT 118800  
GGAGAGCAGT GTGGTAATAT ACATATTAAC CAATGTATAT ACCCTCTCAT TTTAGAAATT 118860  
CTATATTAGA AATCCATCCT AAGAAAATAA CCAGGGATGT GATCAAAATT TTGAATGCAG 118920  
CAGCACAGTA TTATTTATAA TAGTTATAAA TAAGAAACAA CCTGAATGTC CAGCAACAGG 118980  
CAAAAATGAT AAATAAATTG TGGCATATTT AAGCTGGTGG CTCATGCCTG TAATCCCAGC 119040  
ACTTTGGGAG GCTGAGGCAG GAGGATCTCT TGAGGCCAGG AGTTTGAAAC CTGTCTGGGC 119100  
AACATAACGA GACCCAGTCT CTACAACATA TTTTAAAAA TTAGGTGGGG CATGGTAACT 119160  
CATGCCTGTA ATCCCAGCAC TTTGGGAGGC TGAGGTGAGC AGATCACCTG AGGTGAGGAG 119220  
TTTGAACTA GCCTGGCCAA CATGGTGTA CACCATCTCT AAAAAAATA CAAAAATTAG 119280  
CCAGGGTGGG GTGCGTTCCT GTAGTCCCAG CTA CTGCGCA GACTGAGGTA GGAGAATCAC 119340  
TTGAACCCGG GATTCCGAGG TTGCATTGAG CTGATATCAT GCCACTGCAC TCCAGCCTGG 119400  
GTGAGACCT GTCTCAAAAA AAAAAAAAAA AGAAAAAGAA AAAATTAGCT GGGCGTGGTG 119460  
CTGTACGCCT GTAGTCCCAG CTATCCGGA AGCTGAAGCG GGGGGATTGC TTGAGCCAG 119520  
GAATTTAAGG CTGCAGTGAG CTATGATTGT GCCACTCCGC TCCAGCCTGA GTGAGAAAGC 119580  
AAGACTCTGT CTCTAAAAA AAAAAAAGTG ATATATTTT AAAATAGAGT ATATTACTTA 119640  
TATAGACATC AAAACAATA TTTTCAAGG ATATTTAAAA ACATAGGATC ATGACAAAAT 119700  
GTAAAGTTCA AAGGTAAGAT GGAGAATGGA GAACTGTGGG GAACTGTATA ATCTGACAAT 119760  
TCGTAGTTGC ATACATCTTT CTGTGTGCTG GTGCTGTTAG AACACTTTGT ACGCATCACC 119820  
TCATTTAAGT TCAGCATCCC TAGGTGGCAG ATACTATTAT TATATTCCAG TTTTGTTC 119880  
CGTTGTATAT GCGGTGTGAG CCCAATATG GGATGTGTGT GTGCACATGT GCAGTATTG 119940  
GAAAGTTCTA TGAAATATTA TTAGTGGTTA TCTCTGGGAG GTGATTTTTA TTCCTTTTCC 120000  
AGTATGTTCT CAAGCATTTG CTGCAAGCAG TCTTTTGGG GGCAGGGT GAGAGGCAGC 120060  
AGCAGTTTCC CTAAATTACA GATAGAGGGA GGTAGGTGGT TATGCTTGGC CAGATCTCTG 120120  
TCTAGGGGTA GAGGAGTGCC TGTGTGTGGG TAGGGACACC GGCGGGGGGC TTTGCCAAAC 120180  
ACAGTGGAAC TGTCACGCTG GTCTCTCTT TCAACTCTT CACTCACCTG AGAAAAGGGT 120240  
GTCTATGGAC CATGCACACT TCTGTGGGGA ATTTTACAAG ATGTGAATCA TCAGTGATGA 120300  
AGATGCTTTC ATTTAAAAAG AATTGGAGTA CCTGAGATTA GAGATAACTT CTACCCTTTT 120360  
AAAATATTTT TAAAAATTC TTTGCACTGA TTTTCTTCT TCGTTTTTAT GAGTTGTTTT 120420  
CATTTGGGTG GGATAACTCA ATCTACAGGA GAATATTAAG ACTTTTAAA TTTTAAAAA 120480  
TATACTTTCA AATACTTAAT ACATTTGTG TTAATGACA GCCAGCAGAT ATTGACTGAA 120540  
TTGGGCTAGA TGCTTCAGGG ATCTCCCTTC CATTTAAGAC TCTCCGAGAG GCCATTCTG 120600  
ACTGCAGGTC ACTGTATTAT TTTTAATTTT AAAATTTTCT CTTACTTATT TTATTTAATT 120660  
TTATTTTTTG AGACAGAGTC TCACTCTGTC GCCAGGTTG GAGTGCAGTG GCACAATCTC 120720  
AGCTCACTGC AACCTCCACC TCCCGGGCTC AAGCGATTCT CCTGCCTCAG CCTCCTGACT 120780  
AGCTGGGGT ACAGGTGCAG GCCACCACAC CCCGTTAATT TTTGTATATT TAGTGGAGTC 120840  
AGGGATTGCG CATGTTGGCC AGGCTAGTCT CAACTCCTG ACCTCAAGCG ATCCTTCCAC 120900  
CTCAGCCTCC CAAAATGCTG GGATTACAGG CCTGAGCCAC CCCACTCGGC CTACTTTATT 120960  
AATCCACTTG CAGAAACAGG ATATACACAA AAACGTTTCA AGGCTGTAAG TGCCACTGCA 121020  
TGGCACCAAT GGTAACGTT TTACAAATTT GAGTCAGGAA CAATCATTAG TGCTACTAGC 121080  
AACAAAAATC AAAATTAAT GAAATAAAAA ATTTCTTTCC CCAAATGGCA AAGGAGAAAG 121140  
AAAGGTAATA CTAACACGCA GTCAGGGTGT AGTGAGAGGG CCGCTCTCAC ACAGGACTGG 121200  
TAAGTACAGA GCCATGGAGT AAGCAGGTCT TGAGCTGACA CTGGAGAGGA TCCTTTTTTT 121260

FIG. 6.46

TTTTATTTT TATTTTTTTA GAGTCAGGGT CTTGCTTTTT TACCCAGGCT GGAGTACAGT 121320  
GGTGCCATCA TAGCTCACTG CAGCTTCAAA CTCCTGGGCT CAAGAGATCC TCCTGCCTCA 121380  
GCATCCCCAG TAGCAGGGAC CACAAGTGAG AGGATCCTTT AGTGTGTGCA AGGAGAAGGA 121440  
ACAGAGGTGT GGATGGGTGG GCACAGACAC AGGAGCACAG CTGAAGCAGA GGATTACAAA 121500  
GGGTGGAGCC TGATGTAAAG AAACCTAATA GGTGACAGAG CATGGAGGCT CTTGAATACC 121560  
AGGCTGGAAA CTGCATTAGG AACGGTGCTC ATAATTGCAG AAAATTTTAC ATGGCCTAGA 121620  
TAGTCATCAA AGGATGATGT ACAAACAACAT ATGGCATATT TATACAATGT GCCGACAGGA 121680  
TGCACTGAAC ATTTTGAACA ACAAAGAGAC TTGATAATGG CGAGGTTTTG AGGAGGTGAA 121740  
TCAGGATGCA AAAAAAGCAA ACAACTAATA AAGTTGATTG ATGACAAAACA CTATCAAAAAG 121800  
GCAGCCAGGA GAAAAGCTAC TGGTTACCTC CAGGGAGCTG GTGAGGGAGG CTGGGTGGGA 121860  
GGATCTACCC TTCTGAATTC TGAGGGCACC TCCAGTGTGG CCTCAGAAA GCAGGAGCTT 121920  
CCAGGCTAGA ATCAGATCCC GACATCCCTG TTAATTCCAC GGATTCCACA CCGAGTCAGA 121980  
TTTATGATTT ACTATAGGGT TTTAAAAACC AAATTGCAGG GATGCTAGCC TATCAGAGCT 122040  
TATCTCAGAC ATTGTCCACT AAGGTATACA GAGTGCTGCC TGTTCTTTG GTACCCTAAT 122100  
CAGGAAACCC CATCAGATCT GCTCCTTCCT ATGGGGTAGT GAGTAACACG AAGGCTTACC 122160  
ATCTCACACA GATAACTGGT CATAGGTCCA GCAGAAGTTT AAAACAGAAA ATGAGGAAAG 122220  
CCATGTGATT AACTGCTGCC AGACTGTTTG TGTTACAAAC AGCAGTTCCT TAGGCATTGC 122280  
CTGGGACATG CAATAATTC TGTTACACAA TCTGTGGTAG TTAATGCT GCACGATGAA 122340  
AGCTATCTGA TTTGGATTCA TTATTAGGTG AGCCATCTCG TCTGCAATTT GTTCCACCA 122400  
TTTTCATTTA ACAAATGTAA AAAAGTTTAT TAAGCTCTTA CAAAGTTATG CTGGGCAAAT 122460  
ATGCAAAAGT CCAGATCACC TACCGCAGGA ACTAATCTAG CCTCCTCTCT GGGCACCTG 122520  
TTGTTTGGGG CTGGGCAGTT CTTTCCTGTG TAGAACCATC TAGGGCTGAA TAGGTCATTC 122580  
TGACACCTGG GCACCTCTGC CTGCTCGTAA ATGGGACAAT CAGAAAGGGC CTTATGTTT 122640  
CCAACTTTC TTTAAAGTAG CTGTTCTGAA AACATGGTCC AGGGACCCCT GATTGTCCCT 122700  
GAGACCTTTG AGGGGATCTT CAAGGTAAAT ATTAATGTCA TAATAATACT AATATGTTAT 122760  
CTGTCTTTTT TCACTCTCAC TTTCTCACAC GTGAACAGTG GCATTTTCCA GGTGACAGAG 122820  
TGTGTGATAA TGAACCTAAC TGAATGCAGA AGCAAACATG AGAACCTAGT TTTTCAATC 122880  
AAACCAGACG TGAAAGAGAT TTGCAAAAT GAAAAACAA TGCTATCCTC CTCACAATAT 122940  
TTTTGTTTTA GAAAATAAAG TTATTTTCC TAGAAATGTT TTTGAGTTTA TCAGTCATAG 123000  
GTTTATTATT ATAATTAATA AATGAAATAT ACATACACAG ACATATTTT TAAAGTTCTC 123060  
AGTTTAAATC TCTTTTTTTT TTTTTTTTTT TTTGAGACGG AGTCTCGCTC TGTCGCCAG 123120  
GTTGGAGTGC AGTGGTGCGA TCTCAGCTCA CTGCAAGCTC CGCCTCCCTG GTTCGCGCCA 123180  
TTCTCCTGCC TCAGCCTCCC GAGTAGCTGG GACTACAGGC ACCCGCCACC GCGCCCGGCT 123240  
AATTTTTTGT ATTTTAGTA GAGACGGTGT TTCACCATGT TAGCCAGGAT GGTCTCGATC 123300  
TCCTGACCTC GTGATCTGCC CACCTCGGCC TCCCAAAGTG CTGGGATTAC AGGCGTGAAC 123360  
CACCACGCCC GGTCTCAGTT TTAATTTCTA ATACAGTAAG TATTGATCAG TGTGCCCCAC 123420  
ATTAGTAAAA GCTCTTGGGG TCCTCAGTAC TTCTTTTAA GAGTTGTCAA GGAGTCCTGT 123480  
GACCAAAAAT AGGAGAGCCA CTGCCCTAGA AGGACAGCCC CAGCCCGGGT CAGGAACAAC 123540  
TGGGACAGAA CCTACTGCTC CTAGTGGATT GTAATATGAT AGGATTAAAC CTTCAAGGTT 123600  
TCAACTCTTG GCAAGAGTCC ATGAGGGGCC ATGGTTTGTG CTGAGCATTG CTTACTGTTA 123660  
ACAGGAGCAA GTTCCTTAGG CTGGTGAGCC AAGCCAGCCT GACGCTGGCC ATGGACATCT 123720  
TAGTGGGCTG CTTGTTCTAG TGTGGGTTTT CATTTTATGG GAAATGTCAT CTGCTCTAAG 123780  
GCTCTTCTCA TTTGGGGAAA TCACAAGTTC TCAGAATGTT TGTCTCTCTT GTTGGGGGCC 123840  
TCTATAATTA AATTATAAAA CAGAGGTAAT GGTAAAGTAA TGCAAGATTG GACAGAAACC 123900

FIG. 6.47

ACAGAGGATT TAGGGTTTAA TTTGAGTGAG GCAAAGGGGG GATGAAGATG AGCGGTCCTG 123960  
GAGACAAGAA AAAGATTGGA TGAAGCTGGG CACGGTGGCT CACGCCTGTA ATCCCAGTAC 124020  
TTTGGGAGGC CAAGGTGGGC AGATCACTTG AGGCCAGGAG TTTGAGACCA GCCTGGCTAA 124080  
CATAATGCAA CCCCCTCTCT ACTAAAAATA CAAAAATTAG CCAGGCGTGT TGGTGTGTGC 124140  
CTGTAGTCAC AGCTACTTGG GAGGCTGAGG CATGAGAATC GCTTGAATCC GGGAGGCAGA 124200  
GGTTGCAGTG AGCAGAGATC ATGCCACTGC ACTCCAGCCT AGGCAACAGG GTGAGACTCT 124260  
GTCTTCTTTT TTTTGTAGAC GGAGTCTGTC GCCCAGGCTG GAGTGCAGTG GCATGATCTC 124320  
TGCTCACTGC AAGCTCCGCC TCCCAGCTTC AAGCGAGTCT CCTGCCTCAG CCTCCCGAGT 124380  
AGCTGGGATT ACAGGCATGT GCCACCACAC CCAGCTAATT TTTATATTTT TAGTAGAGAC 124440  
GGGGTTTCAC CATGTTGGTC AGGCTGGTCT CAAACTCCTG ACCTCGTGAT CTGCCCCGCCG 124500  
CGGCCTCCCA AAGTGCTGGG ATTACAGGTG TGAGCCACCA TACCTGGCTG AGACTCTGTC 124560  
TTTAAAAAAA AAAGAGAGAG AGGGAGAGAA AGATTGGATG AAACAACAGA GTGGGGAGGA 124620  
CCTGTGAGCT TGGTAGCTTG GTGAAGGCAG GGCTTTATTG GGGGCCTTAG AGGGGATCCA 124680  
ATAAAGGTTT CCAGTCATGG TAGTGACCTA AAGAAAATAG CATTTTAACA TCTTTCATTT 124740  
CATAATAGAC AGTCACAGTT TACAAGACCC TTCCATACA TTCCTTATGA CATCCATACT 124800  
ACAGCCCAGA GGCAAGTTGT GCACTCTCTC CTCTCACAAA TACAAAACT CAGCCTCTAG 124860  
AGGCCAGCGA CCTGCTCAGG GTGATGTGCA ATTCAGGGAT GACAGAGTCG AGGCTCCCAG 124920  
CCAGTGTTT ATCCCTCACA GGCACGTTGC CTGTCAGTGT GCAGTATAAA ACTTTGTACA 124980  
AGAAATCAAG TTGCATTAGT CAGTCGGATT CCCCAAATGA TCACATTGTA GATGGTGTAT 125040  
GCTGTGGGCA GAGCAAGGGC TGCTGTTTCT TGGGCAAAAC AATCAGTCCC CCTCCCCCCC 125100  
AAAATAATG AATGCCAATG GTGTGACTTT ATTTATTTA TTTTATTTT ATTATTATT 125160  
GTGAGACAGA GTCTCACTCT TTCACCCAGG CTGGAGTGCA ATGGCATGGT CTCGGCTCAC 125220  
TGCAACCTCT GCCTCCTGGG TTCAAGCGAT TCTCCCGCCT CACCCTCCCG AGTAGCTGGG 125280  
ACTACAAGTG CATGCCACTG CACCCGGCTA ATTTTGTAT TTTTTTAAG TAGAGACAGG 125340  
GTTTCACTAT GTTGGTCAGG CTGGTCTTGA ACTCCTGACC TCATGATCCA CCTGCCTCAG 125400  
CCTCCCAAAG TGCTGGGATT ACAGGCATGA GCCACCGCGC CCAGCAATGT GACTTTATAA 125460  
TTACAGAATG TAGGACTCAG CTCCCACTAT TGTTATGACT CAATATTCTC TTAGATAATG 125520  
TTTGGGGCAC TAGCTTACAG GCAGCATTGC CCGGTGGTTA ATGTTGTAGC TTTGCAGGCA 125580  
GACTGACCAT ATTAATAATC GATCACACCA TTTGCTAAGC CTGTGGACTC GGGCAGCCTT 125640  
CTTTCTCTGC GTTAGTTTCC TCCTCTGTAA AACACGGATG ATGCTATAAA CACACCCAAG 125700  
TCCTAGAATT GTTATATGAG TTAGAAAAGA TAGGCAAATA CAACTCTCAC AAGACAGCCT 125760  
GGCCTCCAGT AAGTGCCACT GAGTGTTTGC TCTTATTGTA CAGTGGCTCC AAGTGCTTCT 125820  
GTCTTGATT ATTTCTGACC AGGTGGCTAT GTCTCCTAGT AACTTACCAA TCCTGTTGAG 125880  
TCTTAATAAG CACGTCTTTG ATGCCTACAG TGCGACTGAA TTTCCAGGCC TCATTACTGG 125940  
AGACACAATC ATCCTATATG CTTTTTCCA TTTGTTTTA ATAAAGTGGT ACATGTGTAT 126000  
GGCACCAGAT CAAACAGTAC AGAACAAGTT ACAATGGAAG AGAATGGCCT CCCAGCTTTC 126060  
CTGAAATCCT CAACTCAGAG ACAACTTTTT TTTTCTGAC GGTTTCTTTA TACAGCCCTT 126120  
TTTGTGGTTA CCTTCCTAAC TCTAGAAAAA CTATTCTTAC CTCTGTTTAT TTAATTAGAA 126180  
ACATTAGACG TTACCTTTCA ACTCCTCAGT ATGAAGCTTT AGTTTTCAGC ACCCCAGGCC 126240  
ACCACCTCT TTCCAGGACT TACTACTTAT ACTGGTGGTA GGTGGAATTT TAAATTCAT 126300  
CAGCATTCTT TTGTGATTCT CTGTGTGTTT CAGTTTTACA GCAACCCGTA CTTGTTGCAT 126360  
GAGTACAGTA GAACTGGGAG GCTCATAACT TAGCCTGCAG GACTTTTCAC TTAAGCCTG 126420  
GCCCTCAGGG TGATGTCACC CACCTCATTG TGCTGGCTC AGGAGTTTAG TCCCTCAGTT 126480  
GCCTGGTTGT ATAGTTTGA TGTTACAGCAC CTCCAAATCT CACATTGAAA TGTGATCTCC 126540

FIG. 6.48

AATGTTGGAT GTGGGGCCTG GTGGGAGGTG TCTGGGTCAT CAGGTGGGTC CCTCTTGAAT 126600  
GGCTTGGTGC CTTCCCCATC GTAACGAGTG AGTTCTTGCT CTGGCAGTTC ACACAAGAGC 126660  
TGGCTTTTTA AAGGAGCCTG GCACCTTCCG CTCTTTCTCT TGCTCTTCCCT CTTCCCTTCC 126720  
TTTGTCATA AAAGCTTCCT GAGCCCTCAC CAGAAGCGGT GCAGATGCTG GTGCCATGCT 126780  
TGGACCTCCT GTAGAACTGT GAGCCAAATA AACTCTTTCC TATAAATTAC CCAGTTTCAG 126840  
GTATTCCTTT ATACAATGCA AAACAGACTC ACACATCTGG TAAACCCAG TTGTTTGCTT 126900  
CTAGGTAAGA CGGGAGGAGT GGGGAGCTGG TGAGGGTTTC CACTGCATTG TCTATTTTCA 126960  
GGCAAGGTGT CTCCACTGAG TAGGCTTCAC ATTCAGAGCT CTGGGTAAGG TGGGCAGGAA 127020  
GAGGGTTGCA GGCTGCCCAA AGGAGGGAGA GAAGAAGGCT GAATCCTTCA GTGACAACCT 127080  
GTGAACCAGA GTCTTAGCTC TCTTTGAATA TTTTGTTTCA TATCTTTGGG TTTTGTTTTA 127140  
TTTTGCCTAG GGGTAAATGC TGACTGCCTG TTCTCTGGAC AGGAATGGAG AAGATGGTGC 127200  
TAGCAGGGTT GCTGTTTATA TGATGACATT CATGCAGTCA CTCTCTTTTC AGCACACTTC 127260  
TTACTTCTGC CCTGGGTTCA GTTGCTGACT CTGAGCCCAG AAACCTTCTA GGGTTCTGTT 127320  
AGGTAGATTG GCTTCCACCG TCTTTGCGAC AACCACAGAA AATTCTAGAC TGTTTTCTCT 127380  
TCGGGCTTCA TTAGTCAACT TGCTTCAGTC TGTCTTGCAT CTTCTAAATA TTTATAGATC 127440  
TCTCTCTTTT GTTGGAGTGG CAGAAAATGC TAGTTGACCA CCCAATATTC AAATTATCCT 127500  
GCCTCCTTAA TAACAGAATA TCATTGGATG TGGTGGGTAA ATAATATACC CTAACCTTCC 127560  
TTGCAGAGAG GGGTGGCCAA TGAGATGGAA ATGAAAGTCA TTGGGAAAGA CTCCCAAGAC 127620  
ATCTCTTTAA ACAAGACAGA CTGAAGCAAG TTGACTAATG AAGCCCAAAG CTAGCAGTTG 127680  
TTTTTGTTTA TCTTTGCCTC TTTCTTCTTC TTCCTGTGGG GACAAAGGGC AGTGATATCT 127740  
GGAGCTGCAG CAGCCATTTT GGCATAATGT TGGAAAAGCC AAGAGACTCT CAGAGACCGC 127800  
AGCTCCAGCA GTTTTTTATT TTTTCCAAAT ATTTGCTCCA CTGCAGGAGG ATGAGATATT 127860  
CGTGTGTTGTT GCCTTGTGAC TGTAGGAGGA CTGCACTTCC CTGCCTTGTT GTCAAGTTTC 127920  
CCCATGTGGT CTGCTTTGGC CAGTAAACA TGAGTGGGAG AAGCTTGGTG AACCATTGCA 127980  
TGTCTACCAG CTTTTTTGCT CTCTTCCCTT TGGCATTAGA AAGGCATGTC CAGGATGGAG 128040  
TTGTTCTTTC AGCCTAGATT GGGTTATGAG AAGCTAGCTG GGGGAGTCCA GTAACATATA 128100  
AAGCGAGTTA GAAATAAAAC TTTGTTGTTG TAAGCTATAT ATATATATAT ATATATATAT 128160  
ATATATATAT ATATATATAT AATATGTATG TAATATATAA ATACATATTA TACTTTAAGT 128220  
TCTAGGGTAC ATTTGCACAA TGTGCAGGTT TATTACATAG GTATACATGT GCCATGTTGG 128280  
TTTGCTGCAC CCATCAACTG CTCATTTACA TTAGGTATTT CTCCTAATGC TATCCCTCCC 128340  
CAGCCCCCCA CCCTCAACA AGCCCTAGTG TGTGATGTTT CCCTTCTGT GTCCAAGTGT 128400  
TCTCATTGTT CAATTCCAC CTATGAGTGA GAACATGTGG TGTTTGGTTT TCTGTCTTGG 128460  
TGATAGTTTG CTGAGAATAA TGGTTTCCAG CTTCAATCGT GTCCCTGCAA AGGACATGAA 128520  
CTCATCCTTT TTTATGGCTG CATGGTATTC CATGGTGTAT ATGTGCCACA TTTTCTTAAT 128580  
CTAGTCTATC ATTGATGGAC ATTTGGGTTG GTTCCAAGTA TTTGCTATTG TGAATAGTGC 128640  
CGCAATAAAC ATATGTGTGC ATGTGTCTTT ATAGTAGCAT GATTTATAAT TCTTTGGATA 128700  
TATACCCAGT AATGGGATCA CTGGGTAAAG TGGTATTTCA AGTTCTAGAT CCTTGAGGAG 128760  
TCGCCACACT GTCTCCACA GTGGTTGAAC TAATTTACAC TCCCACCATC AGTGATAAAG 128820  
CATTCTATT CCTATGTCTC CACATCCTCT CCAGAATCTG TTGTTTCTTG ACTTTTTAAT 128880  
GATTGCCATT CTAATTGGCC TGAGATGGTA CCTCATTATG GTTTTGATTG GCATTTCTCT 128940  
GATGACCAGT GATGATGAGC ATTTTTTCAT GTGTCTGTTG GCTGCATAAA TGTCTTCTTT 129000  
TGAGTAGTGT CTGTTTCATAT TGTTTGCCCA TTTTGTATG GGGTTGTTTG TTTTTTTCT 129060  
TGAAATTTG TTTAGTTCT TTGTAGATTG TGGATATTAG CCCTTTGTCA GATGGGTAGG 129120  
TTGCAAAAAT TATCTCCCAT TCTGAGGTT GCCTGTTTAC TCTGATGATA GTTTCTTTTG 129180

FIG. 6.49

CTGTGCAGAA GCTCTTTAGT TTAATTAGAT CCCATTTATC TATTTTGGCT TTTGTTGCCA 129240  
TTGCTTTTGG TGTTTTAGAC ATGAAGTCCT TGCCCATACC TATGTCCTGA ATGGTATCGC 129300  
CTAGGTTTTTC TTCTAGGGTT TTTATGGTTT TTAGGTCTAA CATTTAAGTC TTTAATCCAT 129360  
CTTGAATTAA TTTTGTATA AGGTGTAAGG ATGGTTTCCA GTTTCAGCTT TCTACATATG 129420  
GCTGGCCAGT TTTCCAGCA CCATTTATTA AATAGGGAAT CGTTTCCCA TTTCTTGAGC 129480  
TACAGATATT TTGAGTTTGG TTACCACAGT ATTATCTAGT GGAAGTTGAC TTATACAGTA 129540  
TGTAATAGGA TAAATATAGG TGTGTAACAG AATATTAAGT GTTCGTGTTT CAAAGCTGAG 129600  
GGGAAAATGT TAAAAGTGT CACACACTCT AAAAAGAGAT TAGCTAAAC TGCTTCATTA 129660  
ACCACACTTT GGGGAAACCA GTTCTGAGAT TCTTCTCCAT TACTCTGACA GGTTGGACCC 129720  
TCTGGGGAGC AGATCTCAAG ATCAAGTTAT GAGTGCAAGA GGTGTGTTGG GAAGCGATGG 129780  
TTGTAAAAGA ATCCTGCAGT AGCACCAGGC ACAAGTCTGT CCAGGGAGAG GAGGACTTCT 129840  
ACTCTCTACC AGCATCTCTC CTAAGTCCCC TTAGGGGACG GGGGCAAGGA AGTGCTGGGA 129900  
AGGGCAGGGC ATGGTTCCTG GCTAGGACTC CACCCCCCTG GGGCCTGTAC CCACGGACCT 129960  
AGGTGAAGAC AGGCACTCCT GCCTTCTCGC CCAACGGTTG CGTTTCCCA GATCATCCTG 130020  
GCCTGCCACG CCCCCATCTA CCTATTAAAC TCCCCACCT TCCCAAACC CTAGCAGGCA 130080  
GACACACATC GGTGGAAGAA GACAGGAGCG GCTGGACATT GAAAGGACGT CGAGAGGAGC 130140  
ACACCTGCAC ACCATCGACC AGCGGAACGA GGCAGAGTGT GGCTGGAGCA GTCGGAGGGA 130200  
AGCCTGGGCC GCTGACTCCA GGGGAAAACC ATCTCCTTTC TGGCTCCCC CTCTGCTGGG 130260  
AGATACTTTC ACTGAATAAA ACCTTGCCTT CATTCTCCAA GCCACCTGT GATCCGATTC 130320  
TTCTGTACA CCAAGGCAAG AACCTGGGAT ACAGAAAGCC CTCTGTCTT GTGATAAGGT 130380  
AGAGGGTCTA ACTGAGCTGG TTAACACAAG CTGCCTATAG ACAGCGAAAC TGAAAGAGCA 130440  
CACAATAGCA CACACTCATT GGGGCTTCAG GAGCTGTAAT TATCCACCCC TAGACGCTGC 130500  
CATGGGGCGG GAGCCCCACA GCCTGCCCCG CTAGAGGTTT GAGCAGCGGG AACTGAAGA 130560  
AGAGAGCCAC ACCCTCATCG CACGTCCTGC GAGGGAGACA AGGGAACCTT TCCGTTTCA 130620  
CTTCTGCTTG GCTTGAGCTG GCACTGAAGC ACCCTTTTCC CTCCTCACTG AGGGAGCAGA 130680  
GGGGAAAAGC GGTAGAACTA ACAGGCTAAC AATGCTCCTC CGAAAATATA TCGATTTTTT 130740  
GGATCCCTAG AGATAGGTGA TCACGGCAGC CGCGGAGTGC ATTTGGGTCT CCTTTCAAGA 130800  
AAGAACTTGC TGCTCAGCGT TGAAGAATGC AGTTGGCCAA CAGCCTCCAG CTGCTCTGTC 130860  
TTCAGCATCT GCCATGGCAT CTGAGCTGAG GTCATGTTCT TCCTGGGAGG TCCCAGCAG 130920  
AAGGATCACG TGGAAGCTCC ACAAGCTCCA CAGATGTTCC AGGAGAGGAA TAGGCAGCAT 130980  
TTGGAAGACA TATCCTGCCA TAACAGAGGG CATTTGCTAG TAGAGACAAC AACAGCAAC 131040  
AGCCAAGTAA ACAACACAC AAGCACAAG CACTTCTCC CATTTCCTT CATTGATCCT 131100  
GTCCGGGTAG AAGCTGGGGA GGAAGTAGAA TAGGGTGAGG CGGGGTGGG CTGGGGGGCC 131160  
TACACCTTCT TCCTTCCCC GCAGGTCCTG TCCCTGGGCC AGGCTTGAAC TAGGGGAATG 131220  
GGAAAAGCTG TGAAGTGAAT GAGAATTAGG AGTTTTTATT TAGACTGGAC TTGAATTTTT 131280  
TTTTTTTTTT TTTTTTTTTT GAGACAGAGC CTCGCTCTGT CACCCAGGCT GGAGTCCCGT 131340  
GGCGCCATCT TGGCTCACTA CAGCCTCTGC CTCCGGGT CAAGCGATCC TOCCACCACA 131400  
GTCTCCTGAG TAGCCGGGAT TACAGGTGCC TGCCACCATG CCCAGCTATT TTTTTTTTTT 131460  
TTTGATTTTT TAGTAGAGAC AGGGCGTCAC CGTGTGGGCC AGGCTGGTCT CGAACTCCTG 131520  
GCCTCAAGTG ATCTGTCCGC CTCGGCCTCC CCAAGTGCTA GGATTATAGG AGTGAGCCAC 131580  
CACGCCTGGC CTGGACTTGA ATTTTAAATT CTAATAATG AACTACCAGT TAAATTTAA 131640  
AAATGACCAA AAAAGCTATG GGATATGCTG ATGTTTGGCT TTGGGGATAA GGAAAAGATA 131700  
TCTGGTTGAG CGGCATTGAA AACAGTGTAG GGAGAGAAAA ACTCATTCTT GGCTCACCTT 131760  
TTTGAGTCCC ACTATCTCAA TAATCTGATG TTATATGACA CACACACACA CACACGGAGG 131820

FIG. 6.50

AATCCTGGAA GACTCCATAT CAAGGTGGTG ATGAAGGTGA CCAGTGGGTG ATAGGATTAT 131880  
AGGTGTGTGT TTATTTATTT ATTTTAATTA CCTTTTTTTA GAGACAGGGT CTCTGTCATC 131940  
CAGGCTGCAG TGCAGTGGTG TGATCATGGC TCACTGCAGT CTTGCACTCC AGGGCTCAAT 132000  
CCTCCTGCCT CAGTCTCCTG AGTAGCTGGA GCTGCAGTCA TGCACCAACG TGCCCAACTA 132060  
ATTTACTTTA TTTTATTTTT TATTTTTTGT TAAGATGGAA TCTCACTTTA TTGCCTAGGC 132120  
TGGTCTTAAA CTCCTGGTTT CAAGCATTCC TCCTACCTCA GCCTCTCAAA GTGCTGGAAT 132180  
TACTGCACTT GGCCCTATTA TATTTTTAAA AAATTTCAAT AGTTTTAGGG GTAAAAGTGG 132240  
CTTTGGTTAC ATAGATGAAT TGTATAGTGA TGAAGTCTGG ATTTTTAGTG TACCCATCAC 132300  
CCAAATAGTG TACATTGTAC CCAATGAGTA GTTTTTCATT CTCACCCCC ACCTGTCCC 132360  
CACTTCTGAG TCTCCTGATG TCCATTATAG CACCCTGCTT TTGCGCACTT AGAGCTTACC 132420  
TCCCACCTAG AAGTGAGAAC ATGTGGTAGT TGGTTTTCCC TTCCTGAGTT ACTTCACTTA 132480  
GGTCAGTGGC CTCCAATTC ATCTGAGTTG CTGCACATAA CATGATTTC A TCTTTTTTT 132540  
GACTGAGTAG TAGTCCATCT CTCTCTCTCA CACACACACA TACACACACA CACACACACA 132600  
CACACACACA CACATTTATC CACTCATCCA TTGATGGGCA CTTAGGTTGC TTCTATATCT 132660  
TTGCAATTGT GAATTGTGCT CCAATAAACA TACATGTGCA AGTGCTGTTT TTTCTCCCTT 132720  
TTATCCTTCT TTTCTCCCT ATGCTTCCAT AGGTACTGAG AAAGAGTCTT TTTTATATAA 132780  
TTATTTCTTT TCCTTTGGGA AGATACCCAG TAGTGGGATG GCTTGATCCA ATGGTAGATC 132840  
TGTTTTAGT TCTTTGAGAA ATCTCCATAT TATCTCCATA TTGTTTTCCA TAGAGATTGT 132900  
ACTAATTTAC ATTCCCACCA ACAATGTATG TGTTCATTT TCACTGCATC GGCACCAACA 132960  
ACGGTTGTTT TTTGACTTTT TAATAATGGC CATTCTGGCT GGGGTAAGGT GGTATCTCAC 133020  
TGTGGTTTTA ACTTGATTT CCCTGATAAT TAGTGATGTT GAGCATTTAA GAAATATATT 133080  
TGTTGGCCAT TTGTATATCT TCTTTAAGA AATATCTCTT GAAGTTGTTT GCCCACTTTT 133140  
TAATGTGATT ATTTGTTTTT TTTTCTTGCT GATTTGTTTG AGTTCCTTGT AGCTTCTGAA 133200  
TATTAGTCCT TTGTCAGAGG TATAGTTTGC AAATACTTTC TCCCATTCTG TAGGTTGTCT 133260  
CTTTACTCTG TTGGTTATTT CTTTGCTAT GCAGAAGCTT TTTAGAATAA TTAGGTCCCA 133320  
TTTACTTATT TCTGTTATTT TGTTGCATTT GTTTTTGGGG TGTTAGTCAC AAATCTTTG 133380  
CCTAGACCAA TGTCCAGAAG AGTTTTTCCT AGGTTTTCTT CTAGAATTTT TATGGTTTCA 133440  
GGTCTTAGAT TTATGTCTTT AATCCATCTT GAATTAATTT TTGTATATGG TGAGAGATAG 133500  
GAACCCGTT TCATTCTTTT AACTACATG TGGCTATCCA ATTTCCCAAG CACTGTTTAT 133560  
TGAATAGGAT TTCCTTTCCC CAGTGTATGT TTTGTTTGT TTGGCTGAAG ATCAGTTGGT 133620  
TGTAGGTATT TGGTTTTATT TCTGGGTCT CTATGCTATT CACTTTTAT ACCGTTTCCA 133680  
TGCTGTTTTG ATTACAATAG CCTCGTAGTA TAATTTGAAG TTGGGTAATG TGATGCCTCC 133740  
AGATTTGCTC TTTTTTGCT TAGGATTGCT TTGGCTATTT GGACCCCTCT TTGGTCTCAT 133800  
ATAAATTTA GGATTGGTTT TTCTAATTCT GTGAAAAATG ACATTGGTAT TTTGATAAGG 133860  
GTTGCACTGA ATCTGTGGAT TGCTTTGGGT AGTATAGTCA TTTTACAAT ATTGATTCTT 133920  
CTAATCCATA AGCATGGTAT GTTCTCCAT TTGCTTGTGT CATCTATTAT TTCTTTCATT 133980  
AGTGTTTTGT AATTCTCCTT GTAGGGGTCT TTCACCTCCT TGGTTAAGTA TATTCCTATG 134040  
TATTTTATTT TTATTTTTTG CAGCTATTGT AAATGGGATT GAGTTCTTGA TTTGATTTTG 134100  
AGCTTGGCCA TCATTGGTGT ATAGCAGTGC TAGTGATTG TGTACATTGA TTTTGTAACC 134160  
TAACACTACT AAATTCACCT ATCAAATCTG GGAGATTTT GAGGATTCCT TAGGATTTTC 134220  
TAGGTATGAG ATCATATCAT TGGTAGAGGT AGTTTGAGTT TCTCTTTTCC AGTTTGGATG 134280  
CCCTTATTT CTTTCTCTTG CCTGATTGCT CTGACTAGGG CTTCTAGTAC TATGTTGAAT 134340  
AGAAATGGTG AAAAGTGGGC ATCCTTGCTC CATTCTAATT TTTAGGGGGA AATGCTTTC A 134400  
ACTTTTCCCC ATTCATTTTG ATGTTGGCTG TGAGTTTGT ATAGATGATT CTTACTATTT 134460

FIG. 6.51

TGAGATATAT TCATTTGATG CCTAGTTTGT TGAGGGATTT TATCATAAAA GGAGGCTGGA 134520  
TTTTATTGAA TGCTTTTCT GCATCTATTA AAATGATTAC GTTTTTCATT TTTAATTCTG 134580  
TTTATGTCAT GAATCACATT TATTGACTTA TGTTTATTTG TTGCTTACAT CTACTTTCTA 134640  
ATTTTACTAT AATAAACATG TATAATTTTG TTATCAGAAA AGTAAATGTA AAAGTGAGTT 134700  
TTAATTTTAA AACTTGGGCC TAAGTCTTCC TGCCTCCCAA GCCCATTCCC TTCCTGATAT 134760  
CTGGGGCTTC CCTCCTCAAG CCTGCTCTGC AGGATAAGGG GATACAGTCC ACATGCCTGC 134820  
TGCTGGTTTG GCCCATGATA ACCTCCATGG GCAATGTCTG AGCCTCTGCT GTTGAGTTTT 134880  
GCTTTACACA CTCCTGGCAA GGAAAGGATG GCCAACATGG CTTGGACATG GGTTGCTGAT 134940  
AATTGGTGAT GTCTCATGAC TGGTCTGCC TGGAGGGCTT GCTGTAAGTC CCTGATAGGA 135000  
GGAACATGGA CCTGCACAAG AGCAGAACTT ATCTGACACT GAAGAGGACA CTTCAAGAAC 135060  
AGATTATCAA AGTCTAGCTC AGGGAGAAAT ATACTTTAGA GCAGAATGAG GAATGGCGAG 135120  
GCAGCTGAGC TTAGACACAA GCAGAAGGAA ATCCATGGTG AGGGCACAGG CAAGGAAAGG 135180  
GGCTGAGAGA GCATTAGTGG GGGCAGTCAG GGGCAGTGGT CAGGATGCTC GGATGCCAGC 135240  
GTGAACAATC GCATCAAGAT TAAACACCAT GAGGATCGTT AGACTTCCTG TCATATGTCT 135300  
CCAGGTGGTG CTCCAAATAT CCTAAACCAG ATGACAGCAC CCTCCACCC TCTGCTGTAT 135360  
AAGCACATCT GCTCTCCTAT AATCATTCCC ACATAGCAAT TTATCATTTT TATTGATTTT 135420  
TCTTCATTTA ATACACGTAT AAGTGTGTCT TTTATTTTAA AAAATTTGCA TTCCTTTAAT 135480  
TGCTTTGGAG ATTGTGCATT TTTCTCTCTG TTGATTTACT CTGCCAATAA ACATGTAATC 135540  
CTACCATAAG CATGTTTTAC TTGTGTAATC AACCAAAATA AAAAATTTAA AAAGGAATCA 135600  
CTGACTATGA ATTAGACATG TGGATAGGCA CCAGGGTTGC AGACATGGCC CACGTTCTTG 135660  
CATTAACTTG CACTGTGGCT GGGGCATTGG ATGGGTACAT TAAAAGGATT AAAGTAATAT 135720  
AAGGCAGTAT TTATTAAGTG TTGAGTGAGC ACTACAGAAC CCAAGTGCTG AGGGAGTTTC 135780  
ATGCAGGAAG AGATCAAGAG TAACACAGAG AAGAAGAATA GATCAATTTA GCGCATTTCAT 135840  
TTAAAAATTC ACCTTTTGCA TAAGGGGATG TGTCTTTTGT GGGGAGGAGG GGAGTTCCGA 135900  
TTGGCAGTTT GTTCTCAGGG AGCTTGAAGA AGAGATCTTG GAGAGGAGAC GCAGAGAAAA 135960  
CAAATGAAGA AAATGTCAAA ATGGAAGGGG TTGGCCCGGC TATGCATACC TTAGTTAGCT 136020  
TAGGTAGAGT CTAACTTTT ACAAGTGGTT TCAATAGGTG TGTTTGGTCT GGGTTCTTTG 136080  
GGAGGTATCA TAGGAGAATG AAGGCAGGGA GGACGCTTCC AGCACCAAAA TTCAAAGGGA 136140  
AATGATTTT ACATGCATAG CATTGTTTTA CTCTCTTCC ATTTGGAGCA TATCTTAAAA 136200  
ATTCCATTTG GAGCATATCT TAAAAAACCC ATTTCTCTGA CAATGGTTCT AAAAGGGGGA 136260  
AACATCCTTT GCAACAGAAT CATTCAATCT CTCATTATC AACCCTGAT TGTGTACTAA 136320  
GTGTCAGACC TGATCTCCAT CCTGCCTGGT ATGGCACTAG CTTCTGTCTT GAGACAAGCA 136380  
TTGTGATAAA CCATGACCAA AAAAAGGGCA GTTTTATAAA CACAAGTCTG CCAGGCTTTC 136440  
AGCAATTCTA AATTTCTTTT TGCAAGTCAG GCTGGAGTTA ATGGCTCTTT CCTGCAGCGG 136500  
CGGAGATGAC AGGGCTCTCC CACAGTGCTG AGCAGGCAGT TTGAAAGCCC CACTTCCTGT 136560  
CTCTGCATGG GCGAGTGTCC ACTGGAAGCC ACTGAGAGGA AGGAGGGAAA CCTCAGAAAC 136620  
CGGCCCCTGC CTGGCTGCTT CACCCTAGAA AGCCAGGCA GAGGAGGGAA AGGTGAAGTG 136680  
CTGAAAAAGA ATAAAAAGG GGGAACATGA AAAAGAGCAA GAGCAGGAAG GAGGCAGGGA 136740  
CGGGAAAGGA GGGGAAGCAC GGAAACAGCC AATGTCAAGG AGAAGAAAAG ATGGCTGGTG 136800  
GAAAGGAGCT TCCAGGAATT GGGACACAGC CCTGTCTTAT TGCAAAAGAT GGAAACCCTG 136860  
AAGGAGAACA GGAAGGAAAA AGAAAACAAG TCCGTCTGAG CTGGCAGGGT CCACTTTCTC 136920  
ATTCTACAGA TGAGGAAACA GAGGCACAGA GAGGAAGTGG CTTGCCCAAG GGGGCAGATT 136980  
CTTGAAAGGA TCATCTGCAC TCTCTCTCCC TTAATGCATT CTTACCTCTT CTTTACTCGT 137040  
GAGTCAGTCC TGAAGGACAA GCTGCCTGAA GTCCACACA GATGGGCCTG GGGCAAGCAT 137100

FIG. 6.52

CAAACATCCT GGGGGCCCTG GGTGAGGTTT GCTTTTAAAT TCCAGGTCAG GGAAAGGAAG 137160  
GTCTTTAAGT TGTCTGCTCT AAGCTTAGTA ATCCCCCTCA GAGTTATGGG TGCGGTGTCT 137220  
GGGGTAGCCG TTGCGTCTCT GGGCAAATAC CCTGGAGAAT GCAGTGTTGG TTGTCTGAGC 137280  
TGGGGACAGA GTGACAGCAT AGTTGCATGC AGAGCTGGAG GCTCCTGCAG CTGTACAGGT 137340  
AAGGTGCTGA AATTCTCCAC CAACCCCTCC TCTTTGCCCC CAGCACCACG AAGATAACCC 137400  
TCTTTGAATA TGTGGAAGTC TGTTCTCCAA ACTTTCTAAC ATTCTCATGT CAGTCTTAAT 137460  
AGATTGAGCT CAGTTACTGC CTCCTCCAGG AAGTCCTCCT TGTCTGCAAA TCGGCTGCCC 137520  
ACCATGCCGG CTCACTCATA GTTTTAACTC TGTATCTTTC TAATATGCCT TAGCCCACTC 137580  
TGTCAGGATT CCAGTCAGCT TCCTTCTCCT AGACTAGGAG TTGCCTCAGG CCAGGAGGAC 137640  
CAGCCTTGTT CATATCTGTA CCCTGCAAAC CTGTCAATGC CCAAACCTGC TCAGTGCTTT 137700  
GGAGTATGGA ACCAGCCGTC AATGCAGGAA TGTTACACTC TAAGAGTTCC CAAAGGTAGA 137760  
GAGATGAGGG ATGGTGCTG GAAGTGGGAG GTTATTCTAA GGATGGGTAT GGCAGGAAAC 137820  
ACAATTATAG TTCAGGGAGT GGAGTGTCCA GGAGTGGGAG GAGAGGAACT GGGAGAAAGA 137880  
GCAGAGAGTG AAAGTGAGAG CGGGCACAAA GAAAGGGAAA AAGAGTCAGG GATCAACCAA 137940  
AGTGCATGCT TCCTTTTCAG CCCTGCCAGG ATGTGCAGGG CGGCTGCTGT GGACGCGTCA 138000  
AGGCTCAGCC TCAAACATGT CTTCTTCCTT GACTTTTGTC TATCATTCTA AAGCTAGGTC 138060  
ATTTAAAAAG TTCTTTTGTT TTCTTTCCAC CGATACTCTG ATTTCTGACA TTCGCCAAAA 138120  
AGAGGTCAAG ACCCTGGCAT ACCGCCCTAC TAAGATTAAA ATAAATATTA TCCATTGAAA 138180  
CTGTTATTTT TTCCTTAACT GTTATTTGTA GAGTTAAAGA TTCCCATGAT CGCGCTGGCT 138240  
CTAACATCAT TTTTGGCTCT TTTGAGATCA AATTTGCAAT TTGATGCAAA AATAGCTGTG 138300  
ACGCATATGT GTCTGTATGT GTGTGGTTAG GAGATTTTTT ATCATTACAT CTTCTTTTGC 138360  
CCTGCCTTTC TGCTTTCTG TCCTTTTAAT TTGCGGGCTT TTGGCAACCA CAGCACGGGT 138420  
CTGGTTTCCT AGGAGTTTCT TTTGTAGGAT CAAACCGCTA GTTGGCTCTT GGCCCTGTGA 138480  
TAGGGCCCTG GGCTAACTTA TTGGGAAAAT GTTGCTGTAA CCCCTGCCCA GAGGTGCCTG 138540  
TGACATGGGC CGCCATCTTC TCCTCTTCCC TTGGCTTCAG CCCCACCTAG AAACCTGAAC 138600  
AAACATTTTC CTTGACATTT CATAAAGTGT CAGTGGCTCC TCATTTAGCA AAATACATCC 138660  
CAGGGAAGTT CAAAAGTGAA AAAAGGCCGT AACTTCTTCT TCTTCTCAGG GACCTACAGA 138720  
AAATATGTGG CACCTCGGCA GCCTGGCCTG CAGCACTCCC CTCCCCATCG GTGAGTCCTG 138780  
CTACAGTGGG TCCAGGTGTC TGGACGCCCG GCACGCACGG CTCTCTGCAG ACCTCTGGAC 138840  
AGTACCATGG GAGCCGCACA GTCCCTGCCT GTTCTGTCCG GCAGTTCTTG TTTCCAGCA 138900  
CCCTGTCTCA GGTGAGAGGT TCCCTCTTCT GCTGGGCTTC TCCTCCCTGC TGTGAACCCC 138960  
AAATATCTGA GGCAGGTCAA TTTAGGAACC TTATTTTGCC AAAGTTGAGG ATGTACCCAT 139020  
GACACGGCCT CAGGAGGTCC TGAAGACAAG TGCCCGAGGT GATCGCGGCA CAGCTTGTT 139080  
TTATACATTT ATACAGACAT CAGTCAATAT ATGTAAGATA AACATTGGTT CGGTCCCGAA 139140  
AGGCCGGACA ACTCCAAGTG GAGAGGGGGC TTCCAGTTCA CAGGTAGATA AGAGACAAAA 139200  
TGTTGCATTC TTTTGAGTTT CTGATTAGCT TTTCCAAAGG AGGCAATCAG ATATGCATTT 139260  
ATCTCAGTGA GCAGAGGGGT GACTTGGAAT GGAATGGAAG GCAGTTCTCA GTTTAAATTT 139320  
TCCCTTTAGC TTAGTGATTT TGGGGTCCCA AGATTTATTT TCCATTCACT CTGCAGACAG 139380  
GGGCTTCTGT GCATCCAGGG AGCCCCCTCCT CACAGAAGGA AGCAGGCCAT TAATGAGACC 139440  
CAATCCAGCT TCAACCACCT GGTAACAATT AGGACATCAC TTCTCTGAGC AAGAGCTCCT 139500  
GCCTGTCCAT GAGTTATCAA GACATTCCAA TTGTTCTCC ACATCTTTGA CATGAAGACT 139560  
TGAGGGGGTC AGATTTTCCA GGGGGCTTGA TGGCATGTTT TCTTCACTGT TCCCTGCCCT 139620  
GGTCATCCAA GTGACCCTTG GCAGGGAAGA GGCCCCGAGT TGCAGAATCT CTGTTCTCAC 139680  
AAGCCATTGC CAACCCGGAG AGTGGCTTTG CCACTATTCC TAGCATGTTG TTGGCTATTT 139740

FIG. 6.53



CAGGAATGGG AGTATTTGAC TTTTCCCTTT GCAGTGATTG CTGCAAGGAG AGGAATTGAG 139800  
AGACTCAAGT CCCTGAGATA AATATTTATC AACTATTACT GAAAGGGAGT ATGTCAAAGA 139860  
AAAAATGTGG AGAAACTTCA GCTTGAACAC ATAGTTTAAA TCCAGCTTGG GTGTACTCCA 139920  
GTGGGCATGG ATGTATTACT GTTTTGCAGT GCATTCTTCT ATGATCAATA CACAGAAGCA 139980  
AACAGGCCAC GTGGGTAAAC AGTAATTTTC ATTTACCAGG GTGAATATGG AAGTCCTCTT 140040  
GTTTCCATGT CATGATGAAG GAAAGCAAGG ACCATCTTTT GCCAAGGAAC AGTGGCTGTG 140100  
GGGGAAGTGA GGAGATGGAA GGACAAGGCA GTCAAAAGCT TTGGAACAAC TCTTTTTTTG 140160  
AGATGGAGTT TTGCTCTTGT TGTCAGGCT GGAGTGCAAT GGCACGACCT CGGCTCACCA 140220  
CAACCGCTGC CTCCCAGGTT CAAGTGATTC TCCTGCCTCA GCCTCCCGAG TAGCTGGGAT 140280  
TGCAGGTATG CTCCACCATG CCTGGCTAAT TTTGTATTTT TAATAGAGAC GGGATTCTCT 140340  
CACGTTGGTC AGCTGGTCTT GAACTCCCGA CCTCAGGTGA TCCACCTGCC TCGGCCTCCC 140400  
AAAGTGCTGG GATTACAGGC ATGAGCCACC ATACCCGGCC CTTTTTTGGA ATAATTTTAT 140460  
AGGTTTTCAA ACTATTACAC TTACCTTTTT ATATAAGAGA CAGGACATAG TCACTGAACA 140520  
ATCACTCCAG ATTTTAAGTA AGTCCAGGAT GGGATGACAA TGGAACAACC ATGAAATGAA 140580  
AGGAAGAATG TGTCAGTGGT ATGTCCACAC GTCTCCAAAT CTCTCACCTC TGTCAGCTGC 140640  
AAACAGAGCC TGAAATAAAT GTTTCCTCTG TGCACAGCCT CCACAACTTC CTCCCTCCAC 140700  
GTTTCTCACT CACTCCTCTC CAGCACTTCT CTCCGGGTTT TGCTTACAAA CTTGAAACCG 140760  
GCTATGCAAA AATTATAACT GTGGAAATTA TGACAGTGAA AGAGATCAGA CCTAACCGAC 140820  
TCCATCTTGC TTCTAACCTT TAAGCTGTCC TTGTTTATTT TTGGGCTGAA CTAAGTTTGG 140880  
GAAGGAATTC AGTTCATGGT AGAACTCTGA AACAAAATTG ATAATAGCCC TTTCTGAAA 140940  
AGACCCCTT CTTGCCTGGG GACAAGTCTG CCATTGTAGG ACTAACAAT TAACTACAAG 141000  
ATTAGAAAT AAGGTTTAGG GTTCATGCAG CCTCCAGTTC CAAGAGTCTA AACCTCCCCA 141060  
AATTGCTCCT GGGGATAACA TCACTGTTGT AAAAGCTAAG ACCAGTGCTT GAGATATTTT 141120  
GTAGACCCTG CTCTGGATGG ATCAGCTGAC ACCATCCAGA CTGGTAATTT GGCTCAACCA 141180  
GCTCTGCCAT CCCACCCAGG AACAGAAAAA TACTCACTTC ATCACCCCAT GAGTCCATCT 141240  
CTAACCTGAC CAATCAGCAC TCCCTACTTC CCAGGCCCTT ACTCGCCAAA TCTGCCTTTG 141300  
GAGGCAGATA ACAACTTATC TTTAAAAACT CTGATCCCTG AATGCTCAGG AGACTGATTT 141360  
GAGTAATAAT AAAACTCCGG CTCTGCATGA ATTACTCCTT TTCCATTGCA ATTCTCTTGT 141420  
CTTGATAAAT TGGTTCTGTC TAGGCAGCCA GCAAGGCGAA CCCTTTGGGC GGTTACAAAC 141480  
TCATCCTCTG TGAAGAGTA GGAGTTCATG GAGAAATTGG TTGCAAATTA CAAAATTTTA 141540  
TTGTAAGGTC AACTGTCCC AGTGTCCGTC TGTGCAGCGA AGGGCCCCTG CATGGTTTAG 141600  
TGATTGCAAG TTGAGCCTCT AGGGTCAGGT TGTCTAGGTT TCCATCCCAG CTCATTCACT 141660  
TATTATCTGT GTGTTCTTGA GCAAGCTCCT TAATCAATTG AGGCTTTGTC CTTCTGTTTG 141720  
TATAATGATG AGAATAATAA CCTCCACAAT AACCTCATCA TAAGGTTGTT GTGAAGATGG 141780  
ATCAGATAAT ATATATGTAG AGTGCTTATA ACAGTGCTG GCACATAAAA AATGCTCAAA 141840  
AATCTTAAGT GTTATTAATA ATAACTGAC ATATATTTCT TGAGCAGGGT GGTGGTAAAT 141900  
GGGTGTTCTT TTTATTAAGC TTTAAAGTGT GCATAGATCA TATTAATTCT TTTTATGCAT 141960  
ATGATATATT GCACATGCAT GAAAATACAT GCATTAAAAA TAAATGAGCA TTTATGAGAT 142020  
TTAGTTTAGC AGTCACATGT CCCAGGATTA CAAGCCAGCA ATAATGGGTT GGAAAACATT 142080  
CCAACCCATT CCAACCATTG GAAAACATTG CAACCCATCA CTGGACCCAT GTGCCAAACA 142140  
ATGGAACCGC CACAGGTTT CATTCCTTGG TTAATAAAT ATGATTATTA CGGGAATAAT 142200  
ACTGATTCCC TAAGAATTAA TATCTGAGCA AGTTTCTTTT TTTTCTGTC TTCTTGAAG 142260  
ATCAGCAGGT TCTAGATTCA ATGGAGTCAC TAGGATTGAG CCACCAGTAT ACGCCAGTCC 142320  
TCTCCAGAAC GGCCACCTGG TGGTGGGCAC TAAGGCAGTC TCAGATGAGG ACTGATTGAC 142380

FIG. 6.54

TTTTGTGTGA ACTCAAACCTG CCAAAGTCCC TCCCTCACCT TGCAAACCTC AAAGCACAAC 142440  
TTTCAAAGCA CTACTTTCTT TCTTGGCTCT CAATTCTCTG CCTAGAAAAA GGGAGGTGTT 142500  
GGCAAGGATG TTTGTTTAGT TCTGGGCATC AGTCAATGGT ACCCAGATCT TGCTGAACAG 142560  
AAAAGACACA GATTGTGTTT TCTGAGGCAG TTGGTAGTGC TTATTGCTTA TTGCTCTCAG 142620  
GGGCTTCTGC AGCAGTAGAA GGGCCCTCTT CCCCTGCCAT GCCACACTGA GAGGAGCATC 142680  
CTTGAGTCA TGGTTGGAAT CTGTTTTTGT TATGCTAGTC CTCTCCGCA TGCTAGCTGT 142740  
TGCATTGCAG GGATATGTGT ACCTGTTTAT CTTCTCCACT AGGCTCTAAG AAGCCAGGTT 142800  
TCTTAAAGGA AGGAAGCTGA TCTGTTTAT CTTGAAGTCC TCACAGTGAC ATTGCTCAGT 142860  
CAATGTTGAG TGTATGAATG AATAAACGGG AACCATCACG AAAAAGCCGA AAATACAGTG 142920  
GAAAGACTGG ATCATAAAAT CTTCTAAGCA AATTTTTTTT CCTCTTACAC TCCATTCCA 142980  
AATAGATAAA GTATTTTTTA AAATCCTATC AGAATATTCT AACACACTGA GTTGACAGAA 143040  
TAGAGATTTT TAAATGCAGT GTCATTTGGC CAGCCATTG TGAGAATTTA TAAATGTTTC 143100  
AGTAGGTTGA AAACACTATA AAAGCAAGGA CTATGTTTAT ACCCAACAGC TGGCACTTAG 143160  
TATGAATGCT AAATGAAACA TTCTCTTCTC TTTCAAGAGT CAGTCCAACC AGTGACCCTG 143220  
ACAAGAAGGA AGGCACATTT AACTCAATTT AATGAAGTCT TATAGAGCAT CTCCTTCTCC 143280  
AAGTGCTTTG CTAAGGATGG GGTAAAAACA TGAATAAGTC TTGGATTCTG TCCTTCAGGA 143340  
ATTTTCAGTC TTTGGAGGCA GATACATTG CACCCAATA TTATCCTAGG CAGAGTGTGA 143400  
TAAGTACGAT AATAGCAGTA AAAGCTCTAA GTTAGGCAGG AGAGGAGGAG CTCGTAAAG 143460  
CTTATGGGGC CTGGGAGGCT TTCGGCGGAG TAACTCCAG GGGGACAGCT AGGCATCTGG 143520  
CTGCTGGAAT TGGGAGGAGG ATCATTTTAA GTGGCTACAA CTCTGGGTGC ACAGGACTAG 143580  
AGGGTGAGGG CCAAGATGGG AAATTGTGGC AGCCATCTTC CACACTGGGC GCCCGCCGAC 143640  
CCTTGCTTCC TGGTATTCAT ATTATTGTGT AGTGCCCCC AACATTGTAT CAGGGTTGGC 143700  
CTGTGTGACC AATTGCATAT GGTGGGAATG ATGGTGTGTG ACTTCTAAGA CCAGTTCATA 143760  
GAAGATGTGG CCAATTCCTT TACTGTCTTT TTTTGGCA GGGGAGTGCC GAGTTTCACC 143820  
CTTGTCGCCC AGGCTGGAGT GCAATGGTGC GATCTCTGCT CACTGCAACC TCTGCCTCCC 143880  
AGGTTCAAGT GATTCTCCTG CCTCAGCCTC CCACTAGCT GTGATTACAG GTATGCGCCA 143940  
CCATGCCTGG CTAATTTTGT ATTTTATAGTA GAGACGGGGT GAGATCAATG AGGCAGTCAA 144000  
TTGGCCAGCC TGGTTTGA CTTCTGACCT CAGGTGATCC ACCCGCCTCG GCCTCCCAA 144060  
GTGCTGGGAT TACAGGCATG CGCCAACCGC GCCTGGCCCT TACTGTCTT TGGATCAGCT 144120  
GCTCTGGGGC TAGGTCAATC CTTTATGTGA CTGCAGCCCC AGCCAACATC TGGACTGAAA 144180  
CCCATGAGAC ACCCTGAGCC AAAAAAGCCC AGCTAAGACT TCCTGCATTT CTGACCCACA 144240  
GAAACTGAGA AAAGAAATGT TTTGTTGTTG CTTTAAGCCA CTGACTTCTG GGGTCATTTG 144300  
TTTTGCAGAA ATAGATAGCA GATACAGAAA AGCAGGCTGG TGGAACAGTG TGGGAAACAC 144360  
CTTGATTTTC AGGGAGTTGC ACTTTGTTA TGTGCAATGG TGCACTGTTT TTAGAAAGAC 144420  
ACAAAGATGA TAATACTGGT GATGGGCATA ATACGGGTTG TCAAGAGGAG TGAAGAGGC 144480  
GGGGATAATT TAAGAGGCCA CAGCAGTAGT GTGGCAAGAG GTAATGAGGG AATTGAACCT 144540  
GGTGGGAATG GGTGAGATCA ACGAGGCAGT CAATATGGGC AGTGAGTGTG AAGGAGCTGC 144600  
GAAGGATGAT TCTTTGTTT TGAGCTTAGG AACATGAGAG AACCAAGATC TCATTTATCC 144660  
AAAGAGGAAA CACAGAAGTG AGCCCCTGTT TGGGGGCAGG GCTGGGTAGG AGGAAAAGAG 144720  
TGGAGACGTC TATCTCCCCA GGAAGAGAGC CCCCTGCTTC CAGATCCCAG TGGATGGCAG 144780  
GGCACTCGGC TCATTCACAG ACTGGGCTCG TTGAGAAACC TTTCCCTGGA GGGCAGGGCT 144840  
GCTCTGTTTC ACAGCCCATA TCCCTCATGG CCAAGTGTTT CTCGAGTGAC AGTCTCTGCC 144900  
ATCAATATTT TTAGCATGTG GTCTTTCAGA GACTAAAGAG TGGCATCCAT CTCCTGAAAC 144960  
TCCTTCCCCA GCTGACAGCT GGTGACCCGT GGAGGAGGGA GCTTCAGGGA GCCTGATGGG 145020

FIG. 6.55

CGAGAGTCTG TTCCAATGCC AATCCATTGG AAGAGATGAA GTCAGACCCG AGTTTGATAG 145080  
AAAGCCTACT TCCTCCCTTG TATCCAGCTG TGGAGACCTA CCAACATCAA TGCAAACCAG 145140  
AAGCTAACAC CCAGTTCATA TATCCCAAGT GGAAGGAAGC TTCTCGTGGA ATTGTCTTAC 145200  
ATGACAGTAA CATAAATCCT GAAGGTAATA CTTGGCCAGG TAATGTTAGA AAAGAACCCG 145260  
AACATAGGCA TTGCTATTAT AGATCCTAGG ATAGGCCTGA GCAAAAACCTG TCTGGGATTC 145320  
ATAACATGCT TCGTTGCAAT CTGATAGAGG GAGTGAGATC CACTCCAAAT GGAGTCTGAT 145380  
TTGGGGCAAA GCAAAGAGTA TGAAGGAAA CTTGAGAAAAG GGGGACAGCT TCTCAAATGG 145440  
AGTCTGGCCA CAGCTGGGGC TGGAAAAGAG ACATGACTGC GCTTGCAGAG TGGTGAGAAT 145500  
TTGCTGCTAG AATTTTAAAG TTGTGTGTTT TCATTTTAT GATAATGTAA ACTGAGATAA 145560  
GCATATTCTC TGCTATCCCA ATGAGCCCCT CCTCTAGGAG GACTACCTTG CCACCTTATC 145620  
CATAAATGTG TTTATAAATT ATTTTGATGC CAGCTGGTAT TTTTAAAAA GTGGTTTTGG 145680  
ACTCACAAAA AAAACCATGA TGGATTTAAT ACATAACAAA GCATTTGTGT CAAGTGAAGG 145740  
CCAAGTAACA TCTTAGCGTC CTGTGTGAGC GAAGGTGTCG TGGCAGTTCA AACAAGAATG 145800  
CCGATGAAGC TGCCCAGGAT GGCCAAGGCC ACCTTGGTGT GTTTGAGGGG AATTAGAGTT 145860  
TAGAAAAAAA AAAAAGGCA CCTGACACTC TGAACAAATG TGGTTACCTG GAATTTTGGG 145920  
GTTTTGAAGC TTTGCATTTA ATTTGCAGCT TATGGCCTGA AGGAAAAGAC AGGTGAAATG 145980  
CATATCCTGG GATGAGTCAC CTGGAGGAGA GGGCTGGGAA GGGGCTGAGC TGCACATGCT 146040  
CAGATCTTCT CCCAGGCTTA TCGACCCAGT GAGTCAAGTC TTCTTCCAAC GGGATAGAGT 146100  
GTGAGAGAGA GCAGGGAACA GAAGCCAGAG TCTCTGTAA ATTTCTCGGT ACATTTCTGT 146160  
TAGAGAATGG AAGTTTCTCT ATCGTAGGAG ACCTTGAGAG CCTGGGATAG AAATTACCCC 146220  
TTTGTCTATG ATTTTCTCC CAGAAATAGC ATGGCCACTG TCACTGCTAA GCTGGAGTAT 146280  
CATGAGCACA ATTTCTCTCA CTTTCTATAC CCATGCCTTT CTAGGAGATT GGTGGCTCCA 146340  
TCAAAAAGGA GTTAAAAAGA AGCAGCACTA TTTTGTGGAA TACAATCATC ACCATTATCA 146400  
CCATCAGCAC CACCAACCAG CACCACCATT ATCAAAAGCA TTCACCTGGT GTCTGCCTTA 146460  
CAAAGTCAA ACTGCAGTAG GTATTTGTAA TAGAATGTTT CCTTTCCCCC TTGGGATCTG 146520  
CAGAAAAGCT GGAGAATGTT TTGGTATCAA CACACTAGGT TGCATTGCTA ATCATGTGAT 146580  
GGCCCCATGA CAGTCTCTGT TGGCTGGTGT AGTTCAGGTG GACGACTGCA GGATTTTGT 146640  
CTTGAGCCT CAGTTCTGAC TGGGCTTGGG GTGTAAAAGG TTTGGGAGCC AGATGACAAG 146700  
AGTATTTGAT GGGTAGAATA ATGGGTTTAT CCAAAAGATC ACCAGAATGG TTATTAAATA 146760  
GTACAAAGGA GGAATTTACT GGTAATACCA GTTTGCAAC AGAGAAGAGA GTCTCCAATG 146820  
TGGACTGAAA GTGCTCTCTC TTTGAAGAGG GGAAGGACAG ATTGGGTTTT ATGCCTCACA 146880  
GGACTGGTAC CACATATATT CAGCAGGTTT TTGGGGAAAA TCTATACATA TTTATAAGGT 146940  
GAGCTGATGC CTGCATAATA GATAAACATA TATGTAACAT ACTTTTCATA TTCATTTTGG 147000  
GACTGGGTTT TGGCACTAAA ATTTGTGGAA TTTGGCTCTT TATGTTAAAA GGTGAACTAG 147060  
AGGACACAAA GACGGTTTGT GTGCACCCTC TATAAACTGG CTGAACTGG CTTAAGGTCT 147120  
GCAACTGCTT ATCCAAAAAG AATGTTTGTG AGGCCAGGCC TCTGTCCAGT CAGAGTTGTA 147180  
GTGGTCCAGG TTGTAAATCA AAGTTTATAG CTCTTTTGT TAGAGAGTTC AGCTGTAGGA 147240  
ATTTAGAAAT TTGCCATGCC TGCCAGGCCC TGAACCTTTG ACCCATAGGT AACTTTATTT 147300  
CCTTAACCTT AGGGTCAGTC TTAGTTGATA TGGGGCATCT ATTCTGGTAT CTCAGATCCT 147360  
ATGGTCAAGA GAAAAGATCC TCCACAAGAG GGTCTATGT GGCTGCAAAA ACTGCTCTGA 147420  
GCTAAATCCA CTCAAAATCA CTGCAGGATG TCACTACTAG AAAATAGGGC AGGGATAGGG 147480  
ATCCCCTTCC CATGCTGCCA GAAAATGCCT GATAGCTTAC CTCCCCCGGC CCTTGAGGCT 147540  
CCCTTGAAT AGGCACATGC AATCCCATCT CCACCCAATA GAGCTTGTCC TAGAGCTCAG 147600  
TTTTTCCCA TAGTTTTCCC ACCCACTTGC ACCAGAAAAT CTAATAAAGT CATGTGATTA 147660

FIG. 6.56

ATACAATTCA TTTTATCACG CTTCTGAAGA TTTAAGAGAG AGCGGTCACA TTGGATTCCA 147720  
CAGTACCGAC CTTCTGACGA TTCTTCATTT CACCTTTATC TATTTTTATT TTTATTTTAT 147780  
TTTTTTTTCG AGACGGGGTC TCACTCTGTC ACCCAGGCTG GAGTGCAGTG GGGCAATTAC 147840  
GGCTCACTGC AACCTCTGCC TTCTGTGCTC AAGCAATCCT CCCACCTCAG CCTCCCAAGT 147900  
AGCTGGGATC ATAGGTGCAC ATCACCAAGC CTGGCTAATT TTTTGTATTT TTGGTAGAGA 147960  
TGGGGTTTCA CCATGTTGCC CAGGCTGGTC TTGAACCTCT GAGCTCAAGT GATCTGCCCA 148020  
CCATAGCCTC CCAAAGTGCT GGGATTACTC ACGTGAGCCA CCTCGCCTGG TCCCTTTCAC 148080  
CTTTATTATC TTTGCCTTTA ACTCTAGTGC TTCCTCCCTG AATCAGTTAA GGATTGCATT 148140  
TGGCTGCATT AACAGAAACC TGA CTG CAGA AGCTTAACCA AATAGGGTAG TTTTAAAGA 148200  
GAGATTGCTT ACATCACGCA AATTGCACAA ATTTAAAGTG CATAGTTCAA TGAGTTTTGA 148260  
CAAATGTAGA ATAACATAGC TATATAAAAC CATTCCATCA AAAAAATTTT ATCACCATAG 148320  
GAAATTGTGT CCTGTCCCTT TCTGTCAAT CCCAACTCCT CCCACAAGG CAACCTTCAT 148380  
TCTCATTTCT CTCACCATAG CTTAGTTTTA CATGTTTCTA TAATACAGCA TCATATAAAT 148440  
GGAATAATAC AGAATGCAAT CTTTGTATG AAGCTTCCTT TGGCTCAATG TAATGTTTAT 148500  
GAGATTCATC CATGTTATTG AATGTATCAG TAGTGTTTTC ATTTATATTT CCTAGTGTTT 148560  
TATTGAATAA ATATACTACA ATTTGTTTAT CCACTTATTT GTTGATGAAC ATTTGGACCG 148620  
TTGGCAATTT TTGCCTATTA TGCATAAAGC TGTTAAAAAA CATTCTTGTA CAAGTCTTTC 148680  
ATTTCATATG TTTTCTTTT TCTGAGGTAA ATA ACTACAA GTAGAATTGT TGGGTAATAA 148740  
ATAGGCATCC ATCTAATATT ATAAGCAACT GCACAACAGT TTTTCAACGT GGCTGTAATA 148800  
TTTCACTCTC CCAATAGCAA CGTATGTGTT TTCCAGCTAC TCCACATGCT CACTGGCATT 148860  
TCCTGTTGCC AGTTTAAACA TTTCAGCCAT TCCAGTGGAT ATGAAATCTC TCTGGCTATA 148920  
ATAATGTAT TTCTCTGATG ACTAATTATG TCAAGCCCCT TTTCAAATGC TTATCAGCCA 148980  
CTTCTATACT GTCCTCTGTG ACATGTCCGT TCAATCTTTT TGCTCATTCT TAAAAACAT 149040  
TGGGTTGTTT GTCTTTTCT TAGTTTGTCT TTTGCTTTTC ATTTATAGGA GTACATATCT 149100  
TCGGAATACA AGTCCTTTGT CAGATAAATG TATTGTGAAT AATTTTCTCC TAGTTTGTGG 149160  
TTTGCCTTT CACATTCTTA ATATCTTTT ATGAGTGGAA ACTAACTTTC AAATTATGTT 149220  
CAGTAGATTA ACTTGTTTTT GTTTTGTTTT GTTTTGTTTT TTGTTTTTAA CACTGGGTCT 149280  
CACTTGTTGC CCAGGCTGGA GTGTAGTGGT GCCATCATGG CTCACTGCAA CCTCTGCCTC 149340  
CTGGACTCAA GGGATCCTCC TGCCTCAGCC TCCCAAGTAG CTGGGACCAC AAGCACGCAC 149400  
CACTACACTT GGCTACTTTT TTATATTTT GGTAGACACA GGATTTCGCC ATGTTGCTCA 149460  
GGCTGGTCTG GAGCTCCTGA GCTCAAGCGA TTCACCCACC TCAGCCTACC AAAGTGCTGG 149520  
GATTACAGGC GTGAGCCACC ACGCCCAGTC GAGTAGATCA AGTTTAAATT TTATGGCCAG 149580  
TAGAGATCTA TTTCAAGGCT CTCTATTTT TTCTGTTGCT CTATTTATCT ACCTTTATGC 149640  
CAATTTTCTT CTCTTTTGAT TCAGATAGGG TTATAATAAT AATTATTTT TCCAGGGATT 149700  
AGATGGACCA GGGCTGGTGA AGTTGTTCAA GGGAGTGATC AAGAGCCTGG CTCCTTTCAT 149760  
CCTTCTGTTT CATCTCCTT GGCTCATGGA TTTGTTTTT CAAGTGGCAA GATGGCGCCT 149820  
CCACCTTTGG TATCCTATTT TAGTTCCTGG CAGAAAGAAA GGAACAGGCT AATGGCCCTG 149880  
ATGAGTCTAC CCCCTTTTAA CAGGAGAAAA TTTAAAAAAC AAAAACCATG AAACCCTTTC 149940  
CCAGAGGCAA CAACCAGAAT TCCATTTATC TTTCATTGAC CAGAACAGAC CACATGGTCA 150000  
CTGGTGGTGG CAATGGAGAC TGGGGAGATG AATATTTTAA AGGTGGCATA TTCCAGAAGA 150060  
ACACTGTGCA CTGATTGCAT TAATGAACCC ATTAATGTGC CAAGGGGAGG TTTACCTATG 150120  
AGCATGGGCA AATTAGAACC CACTCTTGGA GCTGCAGGTG AGCCAATCCC ACCTAAACAG 150180  
TGTGGATGCT ACAAGATGGG GAAGTAAATT GATTCTATTC CATACCCTAA CCTCTCTCCA 150240  
AGATGTATTC TTTAAATAGA AGAGGAAGA CAGAAGAAAA CATCCAGAAT ATATTTTAT 150300

FIG. 6.57

TGCTTTTAC TTCTTCAGTG CATTTTAGAT CAGTGCTTCT CAATCTGGCA AGGGGCATGC 150360  
AGGAGGATGT GAGTTTTATC AGGAAACTA CACAACCCC CAACCACAAT GCTACCCCA 150420  
CTCCTGTGGA CCTTCTTAA GAGAGACTCA CTATTATAGA TGGAGTTGAT ACGATTTTAA 150480  
GAGAGGCCAT ATATTATTG CTTTCTGTCT TGAAAACTT GTGATTTTC TGTATTGTGC 150540  
TACTGCCAAA GAGAATAGAA ACCTGACTGA GGTGTCAATG TTTATGTAAC TGATTTCATG 150600  
TACTTTCTGT AGTTCTACCA TTTCTGATGG TTAATAATTT CTTGTGTGTG TGCAGTTGGG 150660  
GAGTGTGTCC TCCTCCTTCT GCTCTTATAC CACACATTAG CACATCAAAA TGCTCTAATC 150720  
TTTGTATGAT TATGTGGCAT GTGGTGATGC AGCCTCAGAG TGGAAAACT TCTCTTGGGC 150780  
CATTGCAAAT GTAACATTTC TTTCAATCAG ATAGTGCCAT TAAGGATTTC ATTATGGCCG 150840  
TCACATCCTG TGACATCTCT AACATGCAG CATTAGGGCC TAAGTGCAGC CCTGCAGGTA 150900  
GAGTTGCCAG GTTTAACAAA TAAAAATTAC ACGCTGGCCA GCGGGGTGG CTCATGCCTG 150960  
TAATCCAGC ACTTTGGGAG GCTGAGGCAG GTGGATCATT TGAGGTCAGG AGTTCGAAAC 151020  
CAGCCTGGCC AACATGGTGA AACCCCATCT CTAATAAAAA TACAAAAATT AGCTGGGCAT 151080  
GGTGCCAAAT GCCTGTAATC CTAGCTACTT GCGAGGCTGA GGCAGGAGAA TCACTTGAGC 151140  
CCTGGAGGCG GGGGTTGCAG TGAGCAGAGA TCACACCATT GCACTCCAGC CTGGGTGGCA 151200  
GAGCGAGATT CTGTCTAAAA AACAACACCG TATTTGGGGC ATGCTGATAC TAAAAAATTA 151260  
TTCATTGTTT GTCTGAAATT AAAATTTAAA TTGGGGGCCC TGTATTTTAC TGGGCAACCC 151320  
ATTTGCAATA TCAGCAACAA TCTCTTATTC AGACCACTGA TTAAGTGTGC AAAATTTGAA 151380  
TCTCTGAACA GTACCTATGT CCTTGATATC TTAAATTAAT GAGTGTCTTA GACACTCAA 151440  
GCAGGAGGAA GCATTATGGC AGATGTTTGA GCCCCAGAGA TGTCCATGAG CACAGCATAG 151500  
AGCTCAGAGC CTCTTTTATT ATTTGCTTCA CGACAGAGCA AAGGACTGCA GCAGGTTGAC 151560  
TGATATAAAA GTTTTACCAT GTCTCAGAGC AGGCCTTTC TCAAGTTTCC AGTAAGGATA 151620  
TTGTATCATT TCTTGCCTGC AGTACTTGTA AATCCACTTA CACTGCCTGC TGTTGAGTCA 151680  
TTTGTTCGT CTTGAGTAGC ATGTCATCCT TGTCCTAGA AGATAGTGAG TTTAGAGACA 151740  
GTAGCCAAGC AACAGCAGAG CAGCCTCAAC CAAAACGATT TTCCATTTTG GTGGGATGAA 151800  
TTGAAACACA AGCATCTTCT ATCCAGGGGA GATTTGGGGA TCATAAAGAA TCAATCTGAG 151860  
CTGGTACCAC CATATTGGCT GCTGCATTTT CTAGAGTTGC CGTAACTAGT CTCACAAGCT 151920  
GGGAGGCTTT ACACAACAGA CATGTATTGT CTCATAGTTC TGGATGCTAG AAATCTGGAA 151980  
TCAAGGCTCC AGGGGAGAAG CTGCTCCATG GTTTTCTCTT AGCTTCTGGT GTTGCCAGCA 152040  
ATCCCTGGTG TTCCTTGGCC CGCAGGCGGA TCACTCCCAT CTCTGCCTCC ATTGTCACAC 152100  
GGCATTTTCC CAGTGTGCCT GACTCTGTGT TTCTTCTCAT AAGAACATCG GTCATATTGG 152160  
ATTACAGGCC CGTGCTACTC CATTATGACC TCATCTTAAC TTAACAATT ACATCTGCAG 152220  
TGATCCTGTT TGCAATAAG GTCACATTCT GAGGTTCCAG GAATTAGAAC ATAGACATAT 152280  
CTTTTGGGAA CAAAATTCCA GTGATAACAG TTTCGGAGAC AGACTAGTCC TGGAGTTTGT 152340  
AAGGTGAGCC AGGACCAAGG TGCCAGGATT CTCATTTTGT AAGGTCCAGG AACAAAGTGA 152400  
TGTTAATAGA AAGAACATGT TTTTGTGTGT TTATTTGTTT TTGAGACAGT CTCACTCCAT 152460  
CACCCAGGCT GGAATGCAGT GGTACAATCT CGGCTCACTG CCGCTGCCAT CTCCCAGGTT 152520  
CAAGCGATTC TCCTGCCTCA GCCTCCTAAG TAGCTGGAAT TACAGGTGTG TCCCACCATG 152580  
CCCAGCTAAT TTTTGTATAT TTGTGTGTGT GTGTGTGTGT ATATATATAC ACACACACAT 152640  
ACATACATAT ATATACATAC ATATATATAT ACACACACAC ACATATATAT ATATATAAAA 152700  
TATATATTTT TTTTAGTAGA GACTGGGTTT CACCATGTTG CCCAGGCTGG TCTCGAACTC 152760  
CTGCGCTCAA GTGATCCACC TGTCTTGAC TCCCTAAGTG GTGGGACTAC AGGCACAAAC 152820  
CACCACGCCC AGACAGAAGG AATATGTTTC CTTCCAGTCT CACTTGACTG GCTGCTTCCC 152880  
TAGATAACAA CAGAGGATGT CTGTTGCAGT TCTCATTGCT GGGGAGTCTA AACTGGAATA 152940

FIG. 6.58

AAACACCCAC TATCTCCATC AGGCTTGCAC TAGAGCCCAG CTCTAGCTGG AGAGAAAGAA 153000  
GCTAACCCGC ACAGACACAG GACTGTAGGC AGGGAGCATC CGGGGGTATT TGGGTCCTGG 153060  
CTCTGATGTG CCTAAGGCCA ACTTCTCTCT GGCCATGCTG GCGTGCATGA GCTCACTAAT 153120  
CTTCCTTTTT GCCTTCCATT TTCTCCAATC CTGACTTAGC AAAGGTTGGG CAAAAGAGAC 153180  
TCTGTGTGAG TTCGAGCAA GCCTGAGATG CTGGATTTTC CAAGATACGA GAAGGGGCTG 153240  
GGGGCTGGGT GAACTGGTGG TGGAGGAGGG AAGGATTAAT TTCCAAGGA GGGGAAGGGG 153300  
CCAGGACATC AGGCCCCGGG GACTTTGAAG AGAGGGTCGT GGGTAGGAGG TAGATCAAGT 153360  
GGAGTGACAC AAAGGTCAGG AAAGAGGAAG TGTCCACACT GTCCTTCGAC AGACTTGAGT 153420  
CTATGGGACT TCCTCCCTGC ACGGTACAAG GAAATGAGTA AGTGAGATAA TGTTGTAAGT 153480  
TCTGGCCCTC TGACATTGCA CTGCCCCGAT GTCACAGTTG GAAACTGTAC CTGCCCCCAT 153540  
CCTTGTCTGG GGTGTGTTTG GTCTGGGGAG GGCTGGTGAA GCAAGAGGTA CTCAGAAAAA 153600  
GGACAGAAAT TGCTTCCTAT TATCTGGGCA TTTGGAGGTG AAGGGGTCAC AGCTCTGGCA 153660  
AAGATGGGGT TGAAAGGGCC CGGACTCCAG GGAGGGGCAG CTCTGCATGG CCTGATTCTT 153720  
GCACCCCAACC TTTGCCCCCT CACACCTCCT CTCATCTCCC GTTTTTGAAG AGGAGGACCC 153780  
TGTCACATCT GGACAATTCT GCAAGAACTC TGTAGAACTG ACTTCACTGT GAACCAGGCT 153840  
CCAGAAGTCA ACAGAAACAA AAATGCTCAC ATTTAATCAC GATGCTCCCT GGCATACACA 153900  
GAAGACTCTG AAAACTTCTG AATTTGGGAA ATCCTTTGGC ACCTTGGGGC ACATTGGGAA 153960  
CATAAGCCAT CAGTGCTGGT GTGTGTGTGT GTGCGCGCAC ACGCGCATGT GTGTGCATCT 154020  
TCTACCATGC CTCCTACAAA TTTGACCTGG GCCCAGGGCC ATGTTCCGGT GTTTTAAAGA 154080  
ACCGAGGCTC CCAGAAGCAG TATTGGGCAG CTAGAGTGGC CCCAGGATCT ATATCAAAGT 154140  
CTACCTGTTT CTGAACCAA TTTCTTCTAG AATTTTATTC CATAAATCTG AATTATGGTG 154200  
TCAGACTCCT AGCATACACT AAAGGAATC TCTGCCTTGC ATTAATAAC AGGAGTTACC 154260  
CCTGGAGGTA ACTCCTAGCC CTGGCTCTTT AGAGAACAGA TGCCGAATAG GCATTAGGGG 154320  
ATGTGATGGA TGTGCTAACT TTCAAAAAA AAAAAAAAAA AAGGCCTGAG CTGAGTGCTC 154380  
AGAGATTCAC AAAAAGCTGA CAGCATCTCT CTGTTCCATT GGAAGCTGGG TGATCCTTTC 154440  
TACTCTTTCC TGAGAAAGGC AGTTGGGCAG GAAAAAGCTG TATCTCTGTC CTCACTGAGA 154500  
GGGTTTCCCA GTCTGAGGGT GAAGGATCAG GAGAGGGAGA CCTGACGGGT CGATGTGGGG 154560  
CATCATCCAC TTGAGTGAGA ACCAGAGGGA TCCCGTCATT GCCCAGGGCA GATGCTCCAT 154620  
TTTGGGGGGC ATCATTCACT CTTTCCTGTT CTCCCTGCAT TCCTCTGGCT CCTGCCAGG 154680  
AGAGGTGGCC GCTGGCAAGA GAGCTTGGTG GAGGTGGGAG GTGGGAGGTG GGGGGTGGGG 154740  
GGTGGGGAGT TCTTGAGCCA GGACCTAGCG CATAGTCTCC AGCCTGCTGA TGGCTGTCTT 154800  
GGATGCTTCA AAGGGGAGAA GATCCTAGAT GTGGGAAACA TTGGTGGGCG TTCTGCTGGG 154860  
GCATCTGTAG CCTCTGAGAA GGCTACCACT CTCTCCTAAG CTTACGCCGT CACACCCTGG 154920  
GCACTTGTTG AATGACTTTA CTTAGCTTAC AGCCTCTGGT TCCTGTTGGG AAAGTTAGGG 154980  
CTTGCCACAG TGTTCATTTT CCTTTGCGGG CAACTCCGTT CCTGGCACTT ATCATATTAC 155040  
CCACTGTACT CCCCCTTAG AGCTGTGTCA AGGTTCTGAG AATCTATCCC TTGGCTTGGA 155100  
AGGGGTCATC TCTCTGGCCA GATCATTTCC TGATAGGTCC TGAGGCACCA CAACACATAG 155160  
GAGGCTTGTG CTCTCTCTGG GGTTCACTGC CTGTCTCCTT CTCCAGGTCA ATATGTGACC 155220  
TTGGACCGGT TGCTTGAGTC CCCTGGTCAT TCAGAAACAA TTGGGTTTCC CTGGCTTTGG 155280  
AGCCTGGCAG CCTGGCTTTG AGAACCAGGC TTAACTTGT CACATGACTA TGGCCAAGTT 155340  
CCTGGGGCTC TCCAAGCTTC ACTTCCTCTG TAAAAAGGGC AATAATATAA TACCTGTCTT 155400  
ATTGGGTTTT GTCCATGTTA GATGAGACAT TGGGTACAAA GCACTTGGTC CCGTGCCTGG 155460  
CACATTTACT GCACTTAATG TATGATAGTT TTCTTATTAT TCTAATAAAC AATATGGCTT 155520  
TGGGAGTATA GTTCTGCCAC ATTGCAGTGG CCAGAGTGAA GGTGGTGAGT GCCTTCTGGG 155580

FIG. 6.59

GCCCTGGGAG TCAAGGTTAT CCGCATGCCC TTTCTTGCTT GCTCCTCAGT GTGGCTGCCT 155640  
CTATGTCCAC ACCATGCAGA TGCAACAGGT AGTTTGAACC TCTGAGGCC ACAGTGGGAT 155700  
GGGGAGGCAG GGACATCACT TATGGGGTGG GAAGTCACCC ATCCCCAGG AAATGGCCCC 155760  
AGCTGCCTTT TCCATGACTC CTCTTGAAAC CCTGTGGAGG CCACATTCGT GTTGGGGCGG 155820  
TCTTTCCCAT GAGGATATGT TCAGATGCCG AGGCATTTTG AAAAGCCCTC CATAGAGTTT 155880  
CCTTTCATAA CACATGATCA TCCCCTTGGG CTTCTGGTTT TTTTCTTTC AGGACCTTAT 155940  
TTTCAGGCAA GTGGCCTTTG ACCTCTAAGG CTGTCCTTTC CTAGCTACCG AATCCAGCAT 156000  
TCAAAGTGAT GGAAATATGT ATATATAGTA ATAGTAAAAT ATCAGCACTT AATGGCCTGA 156060  
TAAGAATGTC ACTGCAATGC TGAGTTTGGG CCAACATTTG CCTGCTCCTG CCATTGAGCC 156120  
CGGGCTCCCC TCCAGAGCTG AGCTGCTGCA AGGGATCTGA GTAAGTAGGG CTGTGTCAGA 156180  
GTGGCGATGA CAGCCACCAC ATGCTAAGGA AGAGATCCCC AAGGACAAGG AGAATCCCAC 156240  
GTGGAGCTAC TTGCTTCTTT GTCAGTCTTG TTTTCTTAT TTCACAACCT TCTAAAACAC 156300  
AATCTCTCAA CCTCTATTGT TAGCTTGCAT TTTCAATCA TGAGCACAGC TTTACCTGGC 156360  
TCCATGCTTT GATTGACTCT ACCTGCCAAC ACTGCAACAA CAGGGAAAGG GACACCGGCC 156420  
TCATACCATT AGATGGTGTG TAGCCTGGGC ATGAGGATAA TTA AAAACTC CCAAGGGGAT 156480  
TTAACATGT AACACAGTTT GGAAACCATT GATGTAAGAT CTTCTTACTC AACATGTGCT 156540  
CCAAGGAGCT GTTGTATCAG CTTATCAGAA ATGTAGATCA GGCCGCACTT GGACCTGTAG 156600  
AATCAGAATC TGCATTTTAT CAGATTCCGA CATTATTTGT ATGAACATTA GCTTTTGAGA 156660  
AGTGTGCTT TAAGAGACTA AGGGGGTCAA TCTACCTCAC TTTGCAGCTC TGTGTTCTT 156720  
AGTCATTGGC TAAAATATCA GCCCCCTGC AATGAGCCAT CCTCCCTTGT ATAGTCAGTG 156780  
ATGGCCTGTG AACCTTTAGC CAACTGGAAG TGGGAGGGGA CACAGTCCAC AAAACACTAT 156840  
CCTGACTTTT GACACCAACT ACAAGTCAAG GGGTTCCCCA AACCACCCTG AGTTGTGATA 156900  
ATTCGCTGGG AGATCTGACA GAACTCACTG AAGGTTGTTA TACTCATGGT TGTGATCTCT 156960  
TATAGGGAGG GAATACAGAT TAAAATCAGC CAAAGGAAGA AGCACACAGC ACAGAGTCCA 157020  
GGACAGTGCC TGACATGGAG CCCCTACGGT CCTCTCCCGT GGAGTCACGG ACAGCGCCAC 157080  
TCTCCTGGCA TTGATGTGTG ACAACACACA GGGAGTGTTT CCCACCAGGG AAGCCTTGGT 157140  
GTCCAGGGTC TTTACTGTGG CTCTGTCACA TGAGCACAGC TGAAGTCCCA TGCGGCCGAT 157200  
CTGTTCCAG ACTCTCCACC GCTACACATC ACTCACAGTC CCTGCTCTAA ATCACACACC 157260  
ATGACCCAAT GTCCCCGGGC AAATGAAAAC ACCTCTAGCA GGCAGGACGT TCCAAAGCCT 157320  
TAGAGATCAC CTCTCAGAAG CTGAGGGCAG AAGCCAGACC TCTTTTGGG CAGGGTTAAA 157380  
TTCTTTATTA CTGTTTTTGA AAAAACTCCC AAATTGAGTT TTTCTCTTC ACTTACAGCA 157440  
GCATAACAAC AATCATCAAT GCAGAAGACT TCTGCGAGCA AAGGTGTGGG GGAAAACCCC 157500  
AAGCAGTGGA CACTAGCTGG TGTCTCCAA TTTGATTCTG ATGCTGTCTA CTGGGAGATA 157560  
GTGTCAGATC CTCAAGCCTA AACCTCCTT CTCCCAGTCA GAGGGCTGGC CTTTGGAAT 157620  
TCTGACCAAT CCACTTCAAG TTGAGGTTCC AACCCTCCG CTCTTTGGG TTGGTTGATT 157680  
TGCTAGAGTG GCTCACAGAA CTCAGGGAAA CACAGCTACC AGTTTATTGC GAAGGACATT 157740  
TTAAAGGATA AAAGTAGGCA GATAAAGAGA TGCATAGGGC GAGGTGTGGA AAGGTCCCTA 157800  
GTGCAGGAGC TTCTGTCCAT GTGGAGCGGG GGTGCACCAC CCTCTCAGTA CATGAATGAG 157860  
TTCTCCTTCA CCTGCCTATC AGCCTCTACA TGTTAGCTC CCCAACCCAG TCCTCTTGGG 157920  
TTTTATGGA AGCTTCAAGA CACCCACATT CTTTCCCCAG AGTATAGGGC AAGACCTTCT 157980  
CTGGGGAGGG TTTTAAGACC CACAGTCAGA AAGGTGGGGT GGGGTCAAGA TTAGAGTCCT 158040  
GCCTTGACGG GCAGGTGAAA GGGGTAGGGG GAGTAGGTGA GAAAAATTCT GTTTATTTTT 158100  
TCTTTTTTTT TTTGAGACGG AGTTTCACTC TTGTTGCCA GGGTGGAGTG CAATGGCACA 158160  
ATCTCAGCTC ACTGCAACCT CCGCCTCCCA GGTTAAGCG ATTCTCCTGC CTCAGCCTCC 158220

FIG. 6.60

CGAGTAGCTG GGATTACAGG CGTGTGCCAC CATGCCTGGC TAATTTTGTG TTTTAAATAG 158280  
AGACAGGGTT TCTCCATGTT GGTGAGGCTG GTCTCAAACCT CCTGACCTCA GGTGATCCAC 158340  
TTGCCTCAGC CTCCCAAAGT GCTGGGATCA CAGGTGTGAG CCACTGCATC TGGCCAAAAG 158400  
ATTCTGTTTT TGAGGCCTGC CTCTGAGGTC TAACACACTC AACATTATAA CAAGACTGTA 158460  
GTAAGGGCTA TGGGAGTTAT GAGCCAGGAA CTGTGGATGA AAACCTATCA CAGATATGCA 158520  
TATATATATA TATATATATA TATGCATATC TATAATAACT CCACAACCTAC ACACTGCCTT 158580  
ATTGCTCAGT TCTTCTCTCC ATGTCTCTGA CCCACCCTTG CCCCCTTCCT CCATCCTTTT 158640  
CTCCATTGCA TACCCATCCA CTGTGCCCTT TGAATGCTC ACACCATGAA CTGCAAACCTC 158700  
TCGTGTGGCT TCAGCCTCTT CTCTGAAAGT TCCTCTCACC TATTACTTTC TCTGGAACCT 158760  
GCCATCCCTG CCACCTTCTC AAAAAAGGCC TTTTATTCTC TTCATTCCAC AAAGCTCAGT 158820  
GTCAAAACAT GGGGTTTACA CTGGAAGCTG AGGTCACATC AGTAGCCGGG ATCAGGGTCTG 158880  
CCCTAGCTGC CCAATGCAGC TCCCAGGCCT CCTGTAAAAC CTTGACCTTT GAGGTCATGA 158940  
CAGCCCTCTC CTGCTATGCT CATAGCTGAC CACTGAACTC CTGGACACTC CCTCCCCCAA 159000  
GTTACACAGAG AATGTGGGCA CATGCCTTAC AGTCTTCCCT TGATCCAAAC TACTGCCTTC 159060  
ATCTTGAGTG ACAGCAGCAT CTTTGGATG TCTTGGCCTG TCTAGCTTTA TTTTTTGTG 159120  
TTCTGCCATC AAGTTGCTAC TTCTGTTGCC ATCGTGCCTG TCAGCGCAGT GCAGGCTGTG 159180  
GTGAAATCCC ACGAACTCAG GCATCACACT GACCGGGTCT GAGTCTGTG TCAGTTGTCA 159240  
GCTAGTTGTG CAATGAAGGG AAAGGGACCT AACTTTCCA AGCCTCAATT CACTCATCTA 159300  
TGGCATGGTG ACAATAATGG AGGTTGATTT AAAGTCCTTT GTAAGAATTA AGAGTTATAA 159360  
TAGACATAAA GTGCTGTATC TGGTATACCT AGAAAACATT CCATAAAAGT TAGTAATTGT 159420  
TGGTCATGTA ATGATGACTC TCTAGGCTAG GATTTCAGCT TCATTGCATG CACATGGTGC 159480  
ACTCACAGGG CGTGACCTCT CTCTGTCTCA GTAACCTCAT CTGAGGACCG GGATAATCAT 159540  
ACCGCTTCAA AGGGATGTCA TAAAGATTAA ATAATATGTG TAAGGCTGCT TGCATTTAGC 159600  
TGCATTCAAC AAATATTTCT GTATCTTTCT CCTCATTTCT CTTACTTTC TTGCTTATTA 159660  
TCTGCTCTAG GTATAGATTT CAGAGAACTA AGCTTGTTAC AATCCTTCAT AAAATAACCA 159720  
GGTTGGTTAG GGCATTTCOA AGAGTCAATA CTGTTTAGTG ACTATTCTCT GTTTAATCTA 159780  
TTTTGATTGT CCAGGGTCAT CTTTGTCTAT GTCATAGGTT GTTGGCTTCT TCTAGAGAAG 159840  
TGAGACGATG GACAAGTTCC AAGTGAGTGA GGCGACTGGT CAGGATATTC CGCTGAAAAA 159900  
CTCATGTGAG TTCTAATTCG TGATTGTAAT TCAATCACAG CCTGAGAACA GTAGGACTGT 159960  
AGTTCAAATG CTCTGTTCCC TTTTTTTTTT CCCAGAGGAT AATTTTTTTT TTTCTTTGAG 160020  
ATGGAGTCTT GCTCTGTCAC TAGGCTGGAG TGCAGTGGCG TGATCTCGGC TCACTGCAAC 160080  
CTCCGCCTCC TGGGTTCAAG CAATTCTCCT GCCTCAGCCT CCAAGTAGC TGGGACTACA 160140  
GGCACATGCC ACCACGCCCA GATAATTTTC GTATTTTATAG TAGAGACGGG GTTTCCCTT 160200  
GTTGGCCAGG GTGGTCTTGA TCTCTTGACC TCATGATCCG CCCACCTCGG CCTCCCAAAG 160260  
TGCTGGGATT ACAGGCGTGA GCCACGCGC CCGGCCTCTA GAGGATAATT TTAAATGTG 160320  
CTTTTGCAAT TGGAAAATGT GATTGGCATT TTTTCTAAT TTTCTAATAT GATACGCTGT 160380  
CGGATGCTAT GGATTACTTA AACCTCTGG CTACCTAGAA AGATCTTTAA GTGGTTCTCA 160440  
ACAAGCTTCA TACGCAATGT AAATTGTATT ATCTCTCAGG ATGTGTGAGA ACATCTGTTT 160500  
TTCTTCTAAT GCAGTAAACA TATAAGGGTC TCTTGGGATA TCTTTTAAAT AGACTTAATA 160560  
CAACATTCAG GAATGATAAC AAAATATAAT CACAGTTGTA AGGGAATGTG AGCATTTCAT 160620  
ATTAATAACA TTGGAACCTT ATGTTTAATA CAGTGTTAAA AGTTGACAAA CATGTAGGAG 160680  
TCAGAAAATT CAATTAAAT TATCACAGTA ATATGAATTT AGCCACATCC TGTGTTAGTT 160740  
ATGAAATCCA TTTAACACCA CAAACAGTAA TATTTTATAGC CAGTTTATTC AAAAGGAAAA 160800  
CAGGAACTAA ACCACTTTC TGAATATAT ACTCTGTAA TGTGGTCAGG CTAATTTTGC 160860

FIG. 6.61



TGGGGGAAGG AACTTAAC TTGAATATTT GAATGCCAG TCATTTAATC TGAATATCCT 160920  
ATTTCTTGC ATGTTGCAAA ATTTTGTCA ATAAAAGGCA GAAAAAGAAA TCTCTTCTCC 160980  
ATGCTCATCC CTAAGAGAAT GGGTTGTCTG TACCCTGAGA GCATTTTATG GAGGGGACAA 161040  
CCACTTTTCT AATTTTCCTT CCCACTTCTC TGTGGGCACA AATGCTCTTT GGTTGAAAGA 161100  
GTTGTAATTC AGTCCCAAGA TGAGGTGTGG TTAAGCATC CCTAACCTAT ATCTGGGGAC 161160  
CCCACAGCCA CACACATGGG GGAAATGGAG CTTGTCAATC AGTTCTCCAG CCATTGCACA 161220  
GGGTTTATGG ACTCTTCGTT GATCCACCCC CACGCTTCTT CTCTCTGCTA GCCGAACACA 161280  
CTTCTCTCTT CTTTATCAGG AGGCCATAGG AGAAGGGCAT TCATTTTAA TACACATACA 161340  
TCTGCATCAA GTCTAATTTT GCCATGTCTC AATCCAACTG TCAAATGGGT TGTTTGGGGG 161400  
CTATGGTGCT TATCAAACAT TACTCAAGA ATAGCCAAAA TTAGCCAAGC AAGGAGAAGT 161460  
TCAGCAACGT TCCCAAATGG CCCCACCAA GTACTGTAAG ACTGAGGATA GCTAAAGGGT 161520  
CTTGAGAGGG ACTTCTCAGG CAGTGGCCCC GACATTTATC TGTTTTTTTA AGTGAGAAAT 161580  
CTGAGTACCA TTCTTGACTC CTCTCCTTA CCCCCAACCC CTCCTAAGC CTTGTGCTAC 161640  
TATTTAGTAA ACAGACCCTC AATGCACAAA CTTCTGTCTA AGGCCATGGC CACCACCCTA 161700  
GTCTAATCCA CCATCTCTTC TCTGGAACAG ACCCCAGCTG CTCTCCCTGT CTCTGTGCTG 161760  
GTCTCTCAAT CCATGCTCCA CACTGCAGCC AGAGTGCTCT ACAATGCAAA TCCATTTGTG 161820  
AGACTCCTCC TCTTAAATC CTCAAGTGGC TTCTCTTTCG CCCCAGGATC ATTTTGAAC 161880  
TCCTTAATGG AAGAGGCATG GCCCTTGGG ATGTGGTCC CCAACCCCTC CCACATCATC 161940  
TTTTCAATCA GATTTCCAC TAAATGAAA TTTTTCAGG TCCTCAACTT TATGGTGACT 162000  
TTCTCTTGCT CAGGATCTTT GAACATACTG TTTCTTCTT CTTTTGTAT TTGCAAGAC 162060  
AACACTTCCT CTGGTAAGAT TTTCTGACA TCCTCTATAA AAAAGATTG AGATAGTTGA 162120  
CTACCCAAAA TGTTTCCAT TCATTCCAAG CTCTATTCAA GGCAGTAAAG TGCCCGGCTG 162180  
ACAGATTGCA TTCCTCATCT TTTCTGAAGC TAGCAATGGC CATGCAACAG CATTCTGGCC 162240  
AATAAGATAG AAGTCGAAGT TGAAGGGTGG GATTCCAAG AAAGCTCGTT GAAGACATAA 162300  
TTCTCATTT CACTTCTTAC TCTTCTCTT TCCTGCTTCC TAAATGCGG TGCAGATGGC 162360  
AGACACTTCA AAGCTGTCTC AGGCAATCAG GTGATGTTAA GGCAGAAACC AGCTTTATGA 162420  
TGGGTAGAAC AGGAAGAAAG AAGGCACCTA TGTTCTTGT CACCTTGAAC CACACCAGCA 162480  
CTGCCTTGGC TACCCCTGGA ATTCCTTTAA TGAGAGGCAA ATGAGAGCTT ACGTGTTTAA 162540  
GCCATTGCTA TTTTATTTT TTTTGTAT ATGCAAAAGA ACTTAATCCT AACTGATATT 162600  
AACACTAAT GGGTCTATTG CTTGGTACCA AGCCAATGCA TGACACATGG TATATATGCT 162660  
CAGTAAGTAT TTGTTGAATG AGTGAGGCAA TGAAAGAACA TAGAGGATAT ATATAACAGT 162720  
CCTCCTGCCC AGATGTCATC TGATCCTCT TAGGATCTGG GCCATAAAA CTGTATCTGA 162780  
TATAGTTTGA ATATTTGTTT CCTACAAATC TCATGTTGAC ATTTTATCCC TAATATTGGA 162840  
GGCAGGGCCT AGTAGGAGGT GTTTTGGTCA TAGTGATAAA TGGCTTGGTG CCGTTCTCAC 162900  
AGTAACGAGT GAGTTTTTAT TCTAGTGGT CTGCAAGAA CTGATTGTTA AAAGAGCTTG 162960  
GATCCTTCCA CCCCTCTCTC ACTCTTGCTT CCTCTCTCTC ACCTTGTAAT CTCTACAAGC 163020  
TCTTCACCTC CCCTTCTCCT TTTGCCATAA GTGGAAGATT TCTGAGGCCT CACCAGAAGC 163080  
AGATGTTGGT TCCATGCTTC TTGTACAGCC TGCAGAACCA TGAGCCAAAT CAACTTCTTT 163140  
TCTTTATAAT TATCCAGTCT CAGGTATTCC TTTATAGCAA CACAAATGGA CTAAGACAGT 163200  
TTCTAATGCT ATGGTTCCTT TAGTAGGTCA GTGTAAAACC CTGGATCACT CCTGTAACAA 163260  
ATTACTTGA ACTCTTCTCA CCATACATAT TTAATAATAG TTGCCATGTT GAAAATCCTA 163320  
TAAGATCATA TTTTATTTCA AATCCAACAA CTCATTGCTA AGGAGATACA AGAAGCAGAA 163380  
AATACAGAGA GACTAATGTG TTGATGATT TTGTGAGGGA CATAAGGTCT GTGTCTAGAT 163440  
TCATTTTTTT GCATGTGGAT GTCCAGTTGT TCCAGCACCA TTTGTTGAAA AGACTATCTT 163500

FIG. 6.62

TGCTCCACTG TATTGCTTTT TCTCCTTTGT CATAGATATC TGGTCACCTT ACCTTAGAGT 163560  
CACAGATGAA TGGTCCTATT ACTTAACTAC TGAAAATACA GGCCAAAGCA AACAGAGGAA 163620  
TAAGGGATAT ATAATAAGT ATTTGTGTAC TTGACTTGGC TCTAAAGGAA GCATTGCGTG 163680  
TCTGTGTAAG AAGAATGGGT GAGAGTTTTC CACCATTCAA TATTTCTAAT CTTTCTGAAA 163740  
TACAAAGCCA GGACATCCTC TAATCCATAC ATTCCATAGT TTGGTTAATA TAAATTCCTT 163800  
TATTAAATCC TTATTAAATA AAGTTATTTA TGTTTCTATG AAACCTCATT TAACCTCTAA 163860  
GTGAAAAATA CTAAGGAGCT AACTAAACAT CAAACATTTT TAATTTTTTA AATTTTTTTA 163920  
GAGACAGGGT CTTGCTATGT TGCCCAGGCT GGCTTTGAAC TCCTGTGCTC AAGCGATCCT 163980  
CCAACTCAG CCTCCCGAGT AGCTGGGACT ACAGGTGCAT GCCACTGTGC TCAGCTAAAC 164040  
ATTTTTTTGA AATGCTCTTT TAAAATCAAT TTTATTGAAG TATAAGTTAC ATACCATAAA 164100  
AGTACTCATT TTGAGTGAC AGATTGACAA GTTCTGACAA ATGTGAACAA CCATGTAACC 164160  
ATCACCAAAA ATAAAGATAT GAGACATTTT CATTACCCCA AAAAGTTCCC GTGTCCCTCT 164220  
CCAGTCAATA TCCAGCCCTA GCCCCAGCTC CAGGCAACCA CCAATCTGCT TTCTGTGCT 164280  
ATAAATTGTA CTTATCTTTT CTAGTGTTT ATACAAATGG AATCATACAG CATTTACTCT 164340  
TTTGTGCTG TCTTCTCTG CTCAGTGTA TGTTTTGGAG ATTCATCTAT GTTCTGTGCC 164400  
TCAGTAGTTT GTTCTTTTTA TTAAGGATA ATTCCATTAT AAGAATATAC CACAATTTGT 164460  
TTATCCATTT ACTGCCTGAT GGGCATTGG TTGTTTCCAG CTTTGAACCTA TTTTGAATCC 164520  
TAAAAGACTG CCAGTTTGA ATGAGACCCC AGAACAATGA ATGTAGGCTC TGTATACAAG 164580  
TTCAGGCTGC TGGGCAACTT AGGCCCTAAG ACACAATCTT GCCACTTAGG CCTTAAGACA 164640  
CAACTGACAT GATGGTGCTT AAAGTGGCTG TGATGGAAAA GGAGGCTGTT TGGAGCCTTT 164700  
GGAGTGCCTT TATAGGTGAA CCCCAGCATA GCACCTAATG ATTTGGAGCA AAGCTGTGTC 164760  
ATTCCCCAAA GATAACTATT CGCCTTTTGA GAAACATCTT CTAGCTACTA TCAATAATAA 164820  
ACACAGAATG CATCACCATG GGCCACCGTG TTGTCTTTTG ACCTGAGTTT CCATTGTGAA 164880  
CAAGAGTCAT TTGATCCAAG GCAGAAAGTT GGGTGCACAC AGCAGTGTTT CATCATCAAA 164940  
TGGAATATGA GATTGGGCCC AAGTAGGTCC TGCAGACACA AATAAGTTGC AAGAGCAAGT 165000  
AGTACAGGCG CTTGGCCTGG CCAGTACTGT TGCCAAGTTG ACTGCTTCCC CTCAGTCTGC 165060  
ATCTGTGGCT TCATGGGGAG TTTCTATGA CCACTTGATG GAGGAAAAAA CAAATTGGAG 165120  
CATAGTTTAT AGTGCTGGTA CTACCCAAAG TGGCTAGCTG AGGCACTACA TCTCCACTCT 165180  
GGGGTGCCCC TGAAGGACAG TGCCAAAGGA AAACCCCTC AGTGAGCAGA ACTTGGAGCA 165240  
ATACAAGTGG GTGTTTATTT TACCTAGAAG AGAAGATGTC CGTGAGTTAC AGATCTACAC 165300  
AAAATCACAG AGAGTGGTTA ATCGTTTAGT CTGATGGTCA GGGACTTCCA AGAGACATGA 165360  
TTAGAAAAT GGTGACAAGG AGTCTGGGG AAGAGGCATA TGGATACCTC TGAACACACA 165420  
CAAAACATGA GAATATGTAT CCCATATGAA TGTTAACCAA AGAGCAGCCA CAACAGAAGA 165480  
GGATTTTAAA ATCAGCTGAA TAAGATGATT CATTCTGACA GCATCAGCTA GTCTCTTTCC 165540  
CCAGCCACTG TTGCCAGTG GGCTTACATA TATCATGGCC ATGGGGGCAG GGCTATGTAT 165600  
GGACACAGCA ACATGAATTT CCACTCATCA AGGCCAATTT GGCTCCAGCC ATTGCTGAGT 165660  
GCTCAGCCTG CCAAGATAGA AATCTACGCC AATATGGCAC CATTCCCTGG GCTAGAAAAC 165720  
CAACTGGTGG AAGTTGATT ACATTGGACC ATTTCCATCA TGGAAGGGGC AGTGCTTTGT 165780  
CTTCCCTGGA ATAGACATTT ACTCTGGATA TGGATGTGCC TTCCCTGACT ACTACAATGC 165840  
TCTGCCAAAC CTACCATCCA TGGGCTTAAT TTTATTTGTT ATAAAATTTT AACCACCATT 165900  
GCTTCTGACC AAGGAAGTAA TCTTACAGCA AAGGAAGTAC AGATATGAGC TTCTGATCAT 165960  
GGGCTTCACT GGCTCACAG TGAAGCAGGT GGCCAGATTA GAACAGTGGA ATGGATTTTA 166020  
AAGGCTCAGT TACAGCACCA GCTGGGTAGC AACACCCTGC TGGCCTGGGG TTATGTCTCTG 166080  
CAGGATGCTT TAAGTCAGTG ACCAATATAT GATGCTATTT CTCCCATGT CAGGATTCAT 166140

FIG. 6.63

GGGTCCAAGA ATCATGGGGT CAAAATGGGA GTGGCTTTTC TCACTATCAC CCTGGTGTTC 166200  
GGGTAGTAAT TTTTCCTTCC CATTCTGTGA ACTTTGGGCT CTGCTATTGC AGAAATCTTA 166260  
GCTCCTGTGG GGGGAATGCT TCCATCAGGG AATACAATGG TGGTTCCTACT AAACCTGACAG 166320  
CTGAGTTTGC CATCTCCTCG TGCCAGTGAA TACACAAGCA AGGAAGGGGG TTCCTTTCTC 166380  
ACCTAGGGTG ACTGATCCTA ATTACCAAGG AGAAATTGGA CTGCCACTTC ACAATGAGGG 166440  
TGAGGAGTAT GACTCTATG TGTCTGTGAT TAATGTCAAT AGAAAGTGAC ACCAACCTAG 166500  
TACACAGAGG ACTGATCATG GTCCAGGCCC TTCAGGAATG AAGATTTGAG TCACCAGGCA 166560  
AGGAACTTGG ACTCACTGAG GAGGGCATAT TCCAAGGAGA ATATTTTATC TATGTCCATC 166620  
TATGTCCATC TATATTCCAT CTGTGTTCCC CTTGGAATTC CTATTCATGA ACATGGGGAA 166680  
TTCCAAGGGG AATATAGAAT GAGTAGTGGA AGGTAGTTAT AAATGTAAGT CAAAAACCAC 166740  
ACAACCAATT TGAGAAATGA GGAAGGTAAT AGTGTTGAAT ATGTCTTCTT TATCTTGATA 166800  
TAAATGTATT TGTGCATATA TTAACCAGTT TATTTATTTA TTATTATTTT TTGAGATGAG 166860  
CTCTCGCCAT GTTGCCCAGG CTGGTCTTGA ACTCCTGGGC TCAACTGATT CTACCATTTA 166920  
GTCCTCCGAG TAGCTGGGAC TACAGGCATG CACCACCATA CCCAGCTGAC CAGTTTTTTC 166980  
CTATTCTCT ACTTAATTC TCTACTATAC AACATAATAT GTGTTAATGG TAGTAACTT 167040  
TATATCTCAG TATTAAGTCA CAAGATATCA AAAAGGGGAAT GCGACTTAGT TACAAGCAGA 167100  
ATGAATATCA CTCAAAGATG AATAAAGAGA AGAGGGTTAG TGCATTTTCT GTTGATGAG 167160  
AGAAAGTTTC ATTGTTAGGC AGAAGCATGA TTTTGCCTTT TTTTTTTTTT TCCAAGGTCT 167220  
CACTCTGTGG CCCAGGCTGC AGTGCACTGG TCGATCTTG GCTCACTACA ACCTCTGCCT 167280  
CCCGGGTTCA AGTGATTCTC CAGCCTCAGC CTCCAGAGTA GCTGGGATTA TAGGTGCGCC 167340  
AGGTTAATTT TTGTATTTT AGTAGAGAAG GTGTTTCTCC ATGTTGGCCA GGCTGGTCTT 167400  
GAACTCCTGG CCTCAAGTGA CCCACCTGCT TTGACCTCCC AAAGTGCTAG GATTACAGGT 167460  
GTGAGCCACT GTGCACAGTC ACCACGGTCT TTTGGGAGG CAACTTTAGC ATGGTTAAGA 167520  
GGTGCGAATG GATGTTAAGC TAACACCAGG TAAGCCCTGG TAGATGTGTA TTGTGTCAGT 167580  
GGGCCTACGC TGGAGCCATG TTTCCCCAAA TTCACTTTTC CTATGTACCT CTGGATTAGT 167640  
GTGGGCCACT GGAGACATTT CACATGAGAT GAGGAAGGTG GGAGTGAAGG AGCAGCATCT 167700  
TTTTACACTA AGCAGGTCCG GGAGGGCATG TGGCTCTGTC TCACATTGTT GGGAATCTGT 167760  
CCATCATCTG GTTGCTTAG GTCAGTGGGT GAGTTCACAG CTGTTCCAGC TTCTGCTGGA 167820  
AACTCCTTCG GTTTCTCTGA CTGCTCCGTG ATGAGGGCAT CAGATTCTCC TGCAGAAAGC 167880  
CCCAGTGTTG AAGTTGGGGC TTCATGTTGG TGAGTGATAG TTACGGGTTT TAGCCCAACC 167940  
TGTGTTTTCT TGCAATTTT AGTGTCAGCT CAGTCTTGGC GGTTTTGGGT TGTCTTGTCT 168000  
TCCCACACTT CATGCCCTTC TTTCCCTCCT GACAGTCTGC CCTTTAGATT TTAGGATTCA 168060  
GCACCAGCCA CAGAAACAGC AACCTCACTG TTAAGGGTTG AATTGTATCT CCCCCAAAGG 168120  
TAGGTTGAGG CCCTACCTGC CAGGACTTCA GAATGTAACC TCATCTGGGA ATAGCATCAT 168180  
TGCAAAATA ATTAATTAAG ATGAGGGCAT ACTGGCTCAG GATGGGCTCC TAATTCAATA 168240  
CAACTAATGT CCTTCTATGA CAGCCACAGG AAGACAGAAA CGCCAAGGGA GAACACCATA 168300  
TGCTGATGGA GGCAGTGGCA GCTGCCAGCC AAGGATTATA ACCAGAAGTC AGGAAAAAGC 168360  
AAGAAGGAAT CCTCCCTTAG TGATTTTACA GGGAGCATAG CCCTGCTGAC ACCTTGATTT 168420  
TGGACTTTTA TTCCCCAAAA CTGTAAAAACA ATACACTTCT GTTGTTTTAA GCCACTCAGT 168480  
TTGTGCTACT TTGTTATGGC AACTCCAGAA AACAAAAATA CACTCAGACT GTTTAATCAA 168540  
CCTCCATAAT TGCATAAGGT CTAATCCCTA TAATAAATCC CTTAAAAATG TCTGTGTATA 168600  
TATATTTAAA AATATAAAAT ATCTTCTAGT GGTTCTGCAT CTCTGGTCAA TCCCTGACTG 168660  
ATACAGAATA TGTATTTTCA TTTCTAATGA TGAAATACCT GAATGAAATT TCTAGGACAT 168720  
ATGGTAAGTG TATGTTTAGC TTTTAAGAAA CTGCCAATT GGGGAATTG CTTGAGGCCA 168780

FIG. 6.64

GGAGTTCAAA CAGCCTGGGT AACAGTGATA CCCTGTCTGT ACAAATAAA AAATATTAGC 168840  
AGCGTGTGGT GGTGTGTGTC TGTAAGTCCCA GCTACTCAGG AGGCTGAGGT GGGAGATTCA 168900  
CCTGAGCCCA GATCTTTGAA GTTATAGTGA GCTATGATCA CGCCACTGCA CTCTAGCCTG 168960  
GGTGACAGAG TGAGAAAGCT GGTCTCTAAA AAACAAACAA ACAAAAAAGA AACTGTCAAA 169020  
CTCTCCCAA CATGTTGCCA TTTTACATT TACCATTTTA CATTCTTACC AGCAATGATT 169080  
GATAGTTCCA GTTGCTCCAT ACCCTTGCTG ACCATTCCAA TAGATGTATT GTGTTATCTC 169140  
ATTGTAGTTC TAATTTGTAT TTCCCTAGTG ATTAATGATG TTAAACATCT TTTTCATGCAC 169200  
CTATTGGCTA TATGTATATC TTCTTTAGCA AAATATATGT TGTTATTGA AGAGCGGAAG 169260  
TTTTACATT TGATGAAGTC TAATTTATTG ATTTTTTTT TCTTAGATGG CTCATGCTTT 169320  
TTGTGTTATC TAAAAAAAT TTGCCTTCTT CATGGTCACA AAGACTTTCT CCTATGTTTT 169380  
CTTTTGGAAG CTTTATATTT TTAGTTTTTA TGTTTATGTT TAAGACCCAT TTCTAGTTAC 169440  
AATTTGTGTG ATTTTTTGA AGGGTCAAGG TTCATTTTCT TTTCCATAAG AATGTACAGT 169500  
TGTTCTAGCA CCCTTGTTAA AAAGACTTTC CTTTCCCCAT TGAAGTACTT TGTCAAAAAT 169560  
CAACTGAGCA TATATGGGCA TCATGAATTT TAATCCTGTT AGAACTGAAT GTTCCAAGG 169620  
CAGGCCATGC CCATGACTGA CCTCCTTTCC TTGGATTGCC TACAAAACAG ATAAAGCTAA 169680  
GTCTGGAGCA AAGAAATCCA TGTCTAACCT GTATTTTTTT TTTTTTTTTT TTAGATGGGG 169740  
TCTCGCTCTG TCACCCAGGC TGGAGTGCAG TGGCGTGATC CCAGCTCACT GCAATCTCTG 169800  
CCTCCTGGGT TCAAGTGATT CTCCTGCCTC AGCCTCCCGA GGGGCTGGGA TTGTAGGCGT 169860  
GCACCACTAT GCCCATCTAA TTTTGTATT TTTAGTAGAG ATAGGGTTTT GCCATTTTGG 169920  
CCAGACTGTC TTGAACTCCT GACCTCAGGT GATCTGCCTG CCTCGGCCTC CCACAGTTTT 169980  
GTGATTATAG GCATGAGCCA CCGTGCCCGG CCTTAACCTT TGTTTTCTTA CACAACACAC 170040  
TACGTGATGT TTTCCACATG CATGGGTCAT TTGCTTCATT TACGTACAAA TGCATAAGCA 170100  
ATATACTGTG TGGTGTGAGT TTGTGATGGG AAAAGGAAGA AGTTTTGCGG ATACTACACT 170160  
GGCTTCCTGC TATCTGTCTG TGTGAATGGC TATGGACTTT GTCTTCTATT TGTTGCTTA 170220  
GCGCAGATAT GATCAGCTTA CAACTTAAGA TTCTAGAGAA AGAGGGTCAT ATCTGTAAAG 170280  
CACTCTGAGC ATGTGTGAAG TTTAATCAAT AGCATATGAG GTTACAGCAA ATTCACTATC 170340  
TTTGTCTCTT CAGCTATAGA ATGGCATGAG GATTCATCTC AATTAGTTC AATTCTGTTC 170400  
AGAACCATGA GCTAGCTGTT CATGGAAGGA AAGCCCACCT GATTGTGGCC AGGGAAGGAG 170460  
AAACAACACT TTAACCAGGT TGATTTGGTT CTCACAGACA CCATTGGCAT GTGACATCTG 170520  
GAACAGACCA TGCCTGGTCT CTGTTCTGAT CACTTACTAT TCAGCTCAAT ATTGGTCTGA 170580  
ATATTCTTTA GACTGACTGA AATGAAAAGG AACTGTTGTG TAACCATCCA TAATTCCAGC 170640  
CTGTAGACCT GGGCTGTATC TCTATGCCCT GCCTGGCACA GACCCACCT CCTGCTCCTT 170700  
CTCCCTCACC ACCAGTCAAT CCTTGTCTTA ATGAACAGGG AGGGCAACCC TGAATGGGGA 170760  
GTGGAGGGAA GAGATGTCAT GAGATGGCAA CGTGACCCCT GAAGTGAGGA TGAAGGCTAT 170820  
GTGAATGTTG TAGGCTGACA GCCGGGCATA GTGGCCCCGT TGCCATGGCG ATGGAGGCAT 170880  
GTTGATGCGA AGTGTCTGCA CAGCTCCTAG GATTTTAAAC AGCAGCTGGG CAGAGCCTCG 170940  
GCGTCCCTGA ATTGTTGCCC CCCTGAGTCA CTGCTTGGCC CCAGCTGTCC TGATCTCTGT 171000  
TGACAAATGG TTGTCCTTCA CAGTCAAACCT ACTAACAGTA CTCTAATTAA TGAATGTGCT 171060  
AATTATTCTT GCCTACTCCC AGCATATTTG TCTAACTAAC CTGTCACACA CAGATCAGTG 171120  
CAGCATATGC ATAATTACGG AGAGCGCTGG GAGCAGGGGA TGGGTGGGAG AGGGGTGGGC 171180  
TCGCAGCCCT GTCGCTGTGG GATATTTCTT GTAAAGTTAC CTTTGCTAAC GGTGAGATGT 171240  
CGTGGGGATA TGTTATTTCC CGTGAAGTGT ATATGTCTTC CTTTCTTTCC TTTCTAAGAA 171300  
TCTCTCTTCA GGGCTGAGGG GCCATTGCTC AGTGCTTTAG CCTGTGAGGG GATTGCCAGG 171360  
TACAAATGCA GAAGGACCAG GGAGCCCAGG TTCTGAAGAC GATTCCGGTA GCAGCACGTA 171420

FIG. 6.65

GGGTGATTAA AACTCCAGAC TTAAAGCCA GACCGCCTG GGCTTGAACC CTTGTTCTGC 171480  
TCCTTGCTAT GTGGGTCTTT GCCTTGACCA CATTITTTTT TTTTTTTAA GACAGGATCT 171540  
CCCTCTCTTG CCCAGGCTGT AATGCAGTGT TGCGATCACA GCTCACTGAA GCCTCCATCT 171600  
CTACAGCCTC AAGCGATCCT CCTGCCTCAG CCCCAGTAG CTGGGACTAC AGGTCTGTGC 171660  
CACCACGTCC AGCTAATTTA CTTTGTAGA GTTGGGGGTC TTGCTATGTT GCCCAGGCTG 171720  
TTCTCCAACT CCTGGACTCA AGCCATCCTC TAGCCTCGGC CTTCCAAAGT GCTGGGACTA 171780  
TAGGCGTGAG CCACGGTGCC AGGCCCTTGA CCACATTTTT AACCCCTCTG AACCTCAGTT 171840  
TCACTTTCTG GGCAATGGGA GGGGGGTAAT TTGTCCCTCA GAGGGTTGCA CTGAGGGGCA 171900  
AATGTGAGGC TCTGGGTACA ATGCCAGTA CAGACTAGGT CCCCACGACA CAGCCGCTCA 171960  
GCGGCTCCGG ATTCTGGGCT GCTCTGGACT GCGGCCAGGC GGTCTTCTGC GGAATCCGG 172020  
GCAGGCAGGG CGGGCTGCGC TCCCCTCCCC GGCTCTCCCG GTGCCCTTG TCTTTTGT 172080  
CTGTCTCAGC AGCTCTCTAT TAAGATGAAT GGCATTTC AAGGCTTCAC CTCTGATAAG 172140  
TGTTCTCTG CAGCTGCAGC CAGAATCTTA ATGTGCGCGC TGAATTTAA TGGCCGTCTC 172200  
GGCTATTAAC ACGCTCTTCT CGGGTGAAGT GGACTCCCTC CATCCCCGGG CCTCTGCACG 172260  
TGCTCTGCGC GCTGGCTGGG GGTGACTCCA AGGAGCTCAG AGCGGGGTGC CCGGCACCTC 172320  
TCGCCAGGCG CCTTTCGACC TTCTAAAGCG CGAATGGCTG GACTTTTCTC CCATGTGTGG 172380  
GGCCCCAGAA GGTGTGGGGC CCCAGAAGGT GTGGGGTCCC TGCGTTCCAC GGAGCCCGGA 172440  
AGGTTTCCAG TGATGGTGGG GGCTGACCAC GTTGGTCCCC GTGGGTGCTG TTTTCATGTG 172500  
CCGGCAGATT GGGATGAGTT TAAAGACAG AAGCGTGTAG GATAGAGAAA CTTCTTTAAA 172560  
AACTGGAAAT TTTAATCTGG GGATTATAAC TATTGGACAG TCAAGTGCAA GAGTGAATAC 172620  
ACTTCTCACT CCTCCTCCC AATTTTTATT TGCGGGATTA GTCAGTCCCC CTCTGCCACA 172680  
TGATAATTGT GAGAACTACC AGGGTCTTCA TTCTCCTGOC ATCTGGTTGA CCTCTCCAAG 172740  
AATGGACACC CGGGCAGCCT GGGCCAATGA GGCTGTCCTA AGAGTTTAGA TGAGAGAAGT 172800  
CAGTCTTTGA CAGGTGATGG AAGCTGTAAA ATGTAAACT CCACAGTTGG TGAAGATGTC 172860  
TCCAGGAAAC AGGTCTGCAG AGAGAATACG TTTGACATGC TAAGAGAAGC TGAGAGAGAG 172920  
CGAGAGGAGA GATTGGAAGA AAGACAGAGA CAGAGGTAGA GAGAAGGGAA AGAGAGAGAG 172980  
AAAGGGACAG AAGAGAGAGA AAAAGAGGG GGCCGGGCGC GGTGGCTCAC GCCTGTAATC 173040  
TCAGCACTTT GGGAGGCCGA GGCGGGCAGA TCACGAGGTC AGGAGATCGA GACCATCCCG 173100  
GCTAACACGG TGAAACCCCC GTCTCTACTA AAAAATATAA AAAAAATTAG CCAGGCGTGG 173160  
TGGTGGGTGC CTGTAGTCCC AGCTACTGAG GAGGCTGAGA CAGGAGAATG GCGTGAACCC 173220  
GGGAGGCAGA GCTTGCAGTG AGCTGAGATC GCGCCACTGC ACTCCAGCCT GGGCAACAGA 173280  
GCAAGACTCC GTCTCAAAAA AAAAAAAAAA AAAGAGAGGA AGGGCGGGAG AGAGAGAGAG 173340  
AGAAAGCTCT CTAGCTCCAA GGCTTAACCA CATCTCTGTT CTTTTCAACT TCAGCTGTCA 173400  
GATTTTGA CTCTTTGAGT GAATAAATC TCCTTTTGC TTAACTAGT TTGAGCTAAG 173460  
TTTCTATTGC TTGCACTGG AATACTTGT AAGAGGACTG GCCTTCATT CTGATGCATT 173520  
GTCACTAAGA TGTAAGTGT AGAAGAGCTA ACGCTTTATG GGGTTCAAAC TCCTTGCTA 173580  
CCAAAACCTA AACATCCCCT GAAACTTACC AAAGTGCAGG TATGAATTGG ATCTCACTAA 173640  
GGTGAATATA CAAATCTTGC AAGTGCTGAG CCCTAACCAA TCTTGTAATA ACTCTGTGGT 173700  
AGTTAATTT ATGTCAAAT GATTGAGCTA AAAAATGCC AGGTAGCTGG TAAATGTTT 173760  
TTTTCTGGGT GTGTTAGGGA GGGTGTCTT GAAAGAGATC AGCACTGGAA TCAGCGGACT 173820  
AAGTAAAGAA TTCCACCCCT CACCAATATG GTGGGTGTCA TCAATCCACT GAGGGCCTGA 173880  
ATAGAACAAA AAGCGGGCAG AAGGGCAAAT TCCCTCTTCT TCTTGAGCTG GGCCATCCAT 173940  
CTTCTCCTGC CTTGGACAC TGGAGCCCCT TGTTCTCCAG CTTTGGATT CAGACTGGGT 174000  
CTTGACCAT TGCCCTCCAT CTTCTCCTGC CTTGGACAC TGGAGCCCCT TGTTCTCCAG 174060

FIG. 6.66

CTTTTGGATT CAGACTGGGT CTTGCACCAT TGCCCTCCTT GATGCTCAGG CCTTTGAATG 174120  
CAGACTGGTC TCCACCAGCA GCTTTTCTGA GTCTCCAGCT TGCAGATGGC AAACCATGAA 174180  
ACTTCATGGT GTCCATGAGC ATGTGAACCA ATTTCTATTA TAAATCTGCA ATATATATAT 174240  
ATGAGGAGAC TTATTTATAT ATTGGTTCAG TTTCTCTGGA GAGCCTTGGC TAATATAAAG 174300  
TCTATACTCT ACAAAGTGCC CTAGGTACTC AGGGAGTACC CAAGTGTGTC ATGACCAGCC 174360  
CGACAGCCCT GGCTGCTGGC TTCCCCGCAC ACAACTCTGC ACGCTGCCTT CATCAGCCTT 174420  
TCTCTCTCAG CTGAACCGAG GGCATTGAAG CGGGCCTCTG GCACTGTACC TATGAGGGAG 174480  
CAATATCTTC CCCTACACTG ACCTCTTCCG TGCCGAGATG CAGCCCTCCC TGCTGCCACT 174540  
AGTTACAGTG GTCCATGTTC CCTTTCAAAG TGAAGTTTG ATAAAAGCAC CTCTTAACCA 174600  
ATGCCAAATA GCTAAGTCTG GGACAAAGAT TGCAGGTATT TTGCATTTTC CATGTAACCT 174660  
CAGAGGGATT GCCATTCACA CTGATCTGAG CTGCAGAATA CCAGGCAGCC ACCTCACCCA 174720  
CCCAGCAGGT CCACTCTTAT ACTTTCTCAG AAAGCACAGC CACTCTACTC TTATTCAGTT 174780  
GAAAAGAATT TCCAGGAAGG TGTTTCTGCG ATTGCCTCAG AAAAGTCAGT TCCCTTTGGG 174840  
AATTTCCCTT AGGGATCATC TGTAACCCA TTTCTGCCTT TTACCTGAAT TCTTTGGTTT 174900  
GGTTTGAATT CTTTGGTTTA ATTTATGAAT TCCCTTTATT ACTTTTCTCT GAAGAAATGG 174960  
AGATATCAGC TGCCCTCCC CACTGCCATT TATTCCTTCC TTCATTCAA CCTTATGTGG 175020  
CTGCTACTTA CCGTGTGTTA AGTGTTCACT TTTTCTTGG GAATCAAAA AAAGAAGGAC 175080  
AGTATTTGGG GCACAGATCT TTTGGTGTTT TATACATTTT TTTAAAGTTT CATTTTACAT 175140  
TTGTGTGTGC GTGTGTGTGT GTGTGTGAGA CAGTCTTGCT CTGTTGCCCA GGCTGGAGTG 175200  
CAGTGGCATA ATCATTGGCT CACTGTAGCC TCAAAGTCCT GGGCCCAAGC AATCTTCCCA 175260  
CCTCAGCCAC CCAAATGCT GGGGTTACAG GTTTATGCCA CTCTGTCTGA CCTGAAAGTT 175320  
TTGGGTTTAC TTTCCCTTCT TTCTCTTTCG TGAAGTCAGA GATGATGGCA GCTTCCAGAT 175380  
TCTCTGGTGC CTGTGCTGGG CTCGTGCTGG TCATGGTCTT GGGTCCAGGA TTCATTCTGG 175440  
AGACTCTCAG GGAAGTTTCC CATGACAAGG AATGTAGGA GAGTGTGCTG GCTTTGCGTG 175500  
CTCCTCTGCC AAGCCCTGCT TCTCCTGGTG GGACACACTG AACCACAGCC AGGGCATTTT 175560  
GGTGTTAGT TAAAAAAAAA AAAAAAAAAA AAAAAAGGAA GAAGAAGGCA CTGTGTAATT 175620  
GTGCCGGGGA TCTTCAGAAA TTGTAATGAT GAAAGAGTGC AAGCTCTCAC TCCCCTTCC 175680  
TGACAGGGC AGGTTGTGCA GCTGGAGGCA GAGCAGTCCT CTCTGGGGAG CCTGAAGCAA 175740  
ACATGGATCA AGAACTGTA GGCAATGTTG TCCTGTTGGC CATCGTCACC CTCATCAGCG 175800  
TGGTCCAGAA TGGTAAGGAA AGCCCTTCAC TCAGGGAAGA ACAGAAGGGG AGATTTTCTT 175860  
TGATGGTTGT TTGGAAGTCA GGCTTAAACA ATTGTGTCTG TGTGTGCGCA TGCACAAACA 175920  
CTTTTACCTT ATCTTTATTT TCTTCTTTT ATTGAATGT ATAGGGTTGT GTGTATTTCT 175980  
GTGTAAATTT GGGGTTTTCC TCCTCTTAGT CTTTCACTTT TGTGGTGATT ACCAGTCCCA 176040  
TTTTTAGAGC CAGGGCTGCA ACTTGAAGGT TTTGCTAAAA CCCTCACCGA AGTGTCTATG 176100  
ATCAGCATTT TAACTATTAA TTAATGTGGC CAGGCAAGGG GTGGAAGGTG AGAAGACTAG 176160  
AAAGGGAACA TGATATACAC ATTTACTCAG ATACTGGGCT TTTCTAACAT CTGCAGTGCA 176220  
ATTGAAGTTA CCAGTCATCT GCAGTCTAAA AAGAAAGTGA TTTTGGGAGG TCGGTAGAAA 176280  
AAATCATCTT ATTATTTTTC CTCTATATTA CTTTTTCTT TTTTCTCCT GAAGAACTT 176340  
TTTTTTTTGG TGATACCTC TTTTCTCTA GCACGTATAA TTTTGAAGC ATTTTTCATA 176400  
TGCAGTGTAT ACTTCAGAAA GAGAGAGAGA GAGAGGAAAA TTGTCTGTT CAGCGTTTGC 176460  
ATTTCCATTA TTCCTGCTAT TAGTTAAAA CAACAACAAC AACAAAAAAC AAGCAGGATA 176520  
CCTAGATCTG GAAAAGGGAG AATTGTGTAG AGCTGTCTTC CTAAAGTTCT GAGTTAGGGC 176580  
TGCCTCAGAC CACTTTCATA ACTATCTCCA GTGGCTTTGT GTTTTATATT TATTAAGATA 176640  
GAGAAAAAAA GAGTAATTAC TAAGGGCAGC TGCTGTAGCT TTATGGTGAT TACTGAACAT 176700

FIG. 6.67

TGACATGCTG TCACGTTTTT GGAACCTTGA GTATTTAATC ACTTTGGGAT ATTCTATTTT 176760  
CCCCCATCTT GAGTGTGGAC AGATGCTGGT GATGTAGCCT TCTGGGCACA GAGCAAGCCT 176820  
CCCCCTCAGC CTCTGCACCA GAAAGGCTCA GCTTCACACA CTCCAAGTAT GTTTTCTACA 176880  
AGAACTACAC TTTGTGGCTT TCTGACCCAA ACATTTTTAT ACTAAATTAC ACACAACAAA 176940  
GTTGTAGCTC AGAGAGGGAA CAAATGGCTT ATTTAGGCCA CCATTTTCTT GAGCCATTAT 177000  
GATTTACACAG AGGGCTCCCT TGGCCCTGTA AATTGGCAAG GATTCCATTA TTCAACCCGC 177060  
ATACATGTAC AGAGACCCTG CTCTGGCCCA GATAGTATTC TGGGTACAGG CGGATAGAGC 177120  
AGGAAACAAA ACAGCTACAG TGATGGACAG GTCAGCCTGC AGCAATGCCT GCAGTCTCTG 177180  
CAAAGGTAGC TGTATGGGTG GGCAGGTGGC TAGCACTTAT TCAGCTCTGG AAGGATCTCC 177240  
CCTCTGGCCT CTCCCCTGAC ACCCATCAAT AAAACTGAGG AGCATCGGTG GACAGGGGAC 177300  
CTTGCGCCC CTCCCTGCCT GTGCAGTTGG GGCTGAACCC AGCTACGAAG TTTGAGCTCA 177360  
CTCTCTCCAG CTCCCTCTCA ATTCAGAGCT GAACTGTGGG AAGCTTCAGA GCTCTCTGTT 177420  
TCAAGGACAG GTTCTCCTCA CCTCTCCTAA TGGAGGTGCA CCAGGGAACCT GGCCCTGCTC 177480  
TGCCCAGGGC TTTCTCCTGG ACTTTGCCAT CATGGTCTAG CAAACCCTGT TCAGATTGAG 177540  
GTGAGTGGTG AGATTTCGAA TTCTTTTGA CAGATAGGAT TAAGTCTTCT TCTGTGGGAC 177600  
AAGTGGGAGG TAGAGGTAAG ATTAAGATG GCCAAATGTC TGAGTCCTGA CAGCCACAAT 177660  
ATGGAGATCT AGACTTTTTA CAGACCACAG GGCACAGGGG CCTCACTAAC AGAGTTCCCG 177720  
GAAGTGATGA GTGTGCTGGG GGCTTCCTGG TTGAAGAGAC ACTAGAATGG ACCAGCTGGG 177780  
AGCTAATTTT TTGGGCTGGA GTGTGATGGC CTGCACATCA CTGCCTCTGT CCCTCCATTG 177840  
TCACAGCTGC CCCTTAGGAG CCAGCTGAGG CAATTTGTGG TCAGAGTGAC TTTGCACAGT 177900  
TGTCTGCCT GTGTTCAAGG AGGGAGTTTC TGTGGTCCCT TTGAAACCAC AGAAGAGCCC 177960  
CTCGTATAGC TCTCAATGGA GGGGGCAAAA CATTCAAATA ACTCAGGAGA TAACACAACCT 178020  
ATTTGTTTTT AACTGTGAGT TTTTAGGCAA TCACAAAGAT CCAGATGTAT GTCCAAGCCT 178080  
CTCTTTGCAA TTCTAATTAA CCTCAATGTT GCAACCATAG ACCTACCTTA CAGAGTTCAA 178140  
AAAAATATGC AAAAACCTG CCTTTCTTCT TCCTCATACC CCAAATGCC ATTCTGAACA 178200  
TTTCTGTTA GTTAAAAAAA GATTTCCATG GTGTTACCAG GCACTGTACA CAGTCTGTGT 178260  
CCCAAGACAA GGAGGTACAG TTCCACATGC GCCCATGACT GGGTTGGGCT CTGCACTCTC 178320  
TCTATACTTT GAGAGCCTGA TTTTCTGTGA TTGGGCAGAG CTGGCCCACC TGGTGCAATG 178380  
TCCTCCTCTG CCTTTCAAAC ATGTTTTAGT CATCAAGATC TTCAAATTTG TAACCCTTTC 178440  
CAGCTTGATC CAGCAGAATG CAGATTTGGA AAAACAGAAC GAGTTTAAAA TACATGATTC 178500  
TAAGAAACCT GGACCAGAAC TATCAAACT TGGTTCCCA GAGAATATAG CAAATGGGCT 178560  
CATTGGCCAA TACTATGACA TTGGCTTTTG AGAAAAGAAA GGCTTTATTG CAAGGCTGGC 178620  
CAGCAAGGAG ACAGGAGTTG GGCTCAAATC TGTCTCCCCA GTTTGGGGCT TAGGGCAAGT 178680  
TTTAATTACA CAGACGCATT TCTTATGAGT AGCAGGCAGA GAGCCTCCAA CTTCTTCTGC 178740  
CTAGGTACCA GCAGCTTAGA CATGATGCAA ACCTGGGAAG CACATACTGT ATTTGGAGAA 178800  
AGTGATTGGG AAGAAATGTG AGCTGAGGGG AGGGGCTCAG TGCCCCTGAG CTACACTTAG 178860  
TGATGGCAGA GGAAGGATGT CCTCCCGCAG GAGGCTGTTT CACATCTGCT CTGTTGTAG 178920  
GGGGAGCTGG CAGGCATTAG CAGCGGCCCT TTTCCCCCAA GAGAGGCAGC CTCCTCCAAG 178980  
TTTTGGCGAC ATTATGGCCC TGCAATCATA AGGGTTTGTG AGCATAGTGC TAAGGAGGGA 179040  
AATGGAGCTG CTGTTACTAG TTCCACCCCA ACACACACAC ACACACTCAC AAGAAACCTC 179100  
ACAAGCACCG TATTGGAAGA CTTTGCCATC CAACCTGGGA TTTGACAGGC TCTAGAAGCA 179160  
GAATCATAGA CTCATGAAGT TCCCCCAAAG CAGGAATCTT CCTTACAGTA ACCCCCAACC 179220  
ACCCCCCTCC ACCGCCTCCA CCGGCTGCTT CTTCTGAAC ACTGCAGTGT TTGGAAAACCT 179280  
CACAACTTC CAAGCTTGCC TTTCTATTG TTGCATGGAT TGAAAGCTTG CGTTGTGTGA 179340

FIG. 6.68

AGAATGGCGC TTCCTGCTGT GCTTAGTTTT ATCTCATATA ATCTTTGCAC CATTTAATCC 179400  
TTGCACTCAC CCACTCATGC AACTGCCTTT GCAGAGACTG GAGGGGCCGC TGTAGGCTGA 179460  
CCTTTCCTTC ACTGTACCTA TTTTGTTCCC TGCTTTATTC CCCTGCACCC AGGACACTGC 179520  
CTGGCACAAA GACAGGTCTT TATAAGTGTA TGCAAGTGAA TAAAGATATA TATATTATTA 179580  
TTGTTATTTT TGAGACAGTT TCACTCTGTC ACCCAGGCTG GAGTGCAGTA GCGCAATCTC 179640  
AGCTGACTGC AACCTCTGCC TCCCAGGCTC AAGTGATTCT CATGTCTCAG CCTCCTGAGT 179700  
AGCTAGGACT ACAAGCATGT GCCACCACGC CCAGCTAATT TTTGTATTTT TAGTAAGGAC 179760  
AGGGTTTCAC CATGTTGGCC AGGTTGGCCT CCAACTCCTG ACCTCAAGTC ATCCTCCTGC 179820  
CTCGACCTCC CAAAGTGCTG GGATTACAGG CATGAAACCA GCCTAGAAAT ACATACTATT 179880  
ATTTATTCTT GTTTTACAGA TAAGCAAAGT GAGTCATGGA GAATTTGGTT GAAAGTCCCA 179940  
AGGTCAGGAG TCGTGAAGCT GGGATTAAAA CCTAATCATC TGACTTTAGA GAGTAGACAC 180000  
TTGCTCCATG CATATTGCCT CCAATTCATT CATTCAAGCA CTCCCTGCTC AAGAAGTTCT 180060  
TTCTTATGTT GAGCTGAAAT CTGCAGCCCT ATGCGTTTTA CCCAGCAGTC CTGGTGCTGT 180120  
TCCCTAAAAT CACTTAGACT GTGCCTGCTC TTTCTGTGTT TACAGTGTC A GCTGTAATAT 180180  
CCCCCTCTTC GGCCTAACGT TTCTGAAGTC CCTTGCCACT GGGTCTCCTC TCCTCTTCCT 180240  
GTGTTCTTTC TAAGAACACC TATGCAGATA GGTGTCTTCT GTACAGGGAA GCTGTTCTCG 180300  
AGATCCGGGC ATCGACTCTG TTAGAATAAT CTACGTATGA GTTATTTTTT TGAGAACTAT 180360  
GTGTCATTGC TGA CT CATAT TAACTCTGTG GTTAACTAAA ATCTCAAGAT CTCTTTATGT 180420  
TTGTTGAGAA ACTTATTTAA CTTCTCTGGC CCTCCGTTTC CTTCACTGAG CAGTGGAGTG 180480  
ATTGATAACC TCCACCTGTG GTTGCTGAAG GTCTTG CACA AGATGATATA GTTAAAGTAG 180540  
CTAGCAGTGC CCACGTACGG CGGATGCCTC ACAACGGTTT GCAGCCATCT CTCTATCTGT 180600  
GTCTTTGTCT CTCTCTCACA CTGGTTTTGG CTTACTGTTA GCAGCTAGCC GAGATAAGTG 180660  
TGTTTATGGT CTTTGCATGT ATTGTTTCTG TAGCATACTG GAGGATTACA AGAGGTTGGG 180720  
GAGTGAGGGG GCGGTGAGGA GTAGACAAAG GCAGCCAACT CTTCCAAGTT TAGCTTAGAA 180780  
GGAAGGAGCG GTAAACCCTA GTTGAATGTT GGA CTGAAGC AGGTTTGTTT TTGTTTTGTT 180840  
TAAAGGATAG GGAAGATCTG TGCGTGTTC CAGGATAAAG AAAAGGAGAG AATATGATAT 180900  
TAAAGATTCT GGAAGTG GGA GAAGGAGCAA TGAAATACAG ACTTGAAGTC AGTGGCATGG 180960  
ACAGGGTCAA GATCACAGTT AGAGGATGCA GCCTTAGAGA AAAGGAAGGG GCTCGGTTCT 181020  
CTGAGCAAGG AGGGAAAGAA GAGAGGCAGA TGCAGAGAAG TACGGCACAT CGTGCTGCTG 181080  
GTTGTAGAAA TAACCTCTGA CTTTAAATAA AGTCATCCCT CGGTATCCCT GGGGGATTAG 181140  
TTCTATGACC TCCCTCGGAT GCCAAAATTC GTGGATGCTC AAGTCCCTGA TATAAAATGG 181200  
CATAGTATTT GCA TTTAACCC TACACACATC CTCCATATCC TTTTTTTTTT TTTTTTTTTT 181260  
TTTTTTTTTT TTTTGTGAG ATGGAGTCTT GCTCTGTGCG CCTGGCTGGA GTACAGTGGC 181320  
TCGATCTTGG CTCACTGCAA GCTCCGCCTC CCGGGTTCAT GCCATTCTCC TGCCTCAGCC 181380  
TACAGGTGCC TGCCACCACG CCCAGCTAAT TTTTTTTTTG TATTTTTTAG TAGAGACAGG 181440  
GTTTCACCAT GTTAGCCAGG ATGGTCTCGA CACATCCTCC ATATACTTTA AGTAACCTCT 181500  
AGATAATCTC TAGATTACTT GTTTTGTCTT TTTTTTTTTT TTTTCTTTT GAGATGGAGT 181560  
TTCACTCTTG TCACCCAGGC TGGAGTGCAA TGGTGCAATC TCAGTTCACT GCAACCTCCG 181620  
CCTCCTGGGT TCAAGCAATT CTCCTGTCTC AGCCTCCTGT GTAGCTAGGA TTACAGGCCC 181680  
CTCCCCACCC CCACCCCCCA ACAACTGGCT AATTTTTGTA TTTTATAGTAG AGATGGGGTG 181740  
TCACCACGTT GGCCTGGCTG GTCTTGA ACT CCTGACCTCA GGTGATCTAC CCGCTTCAGC 181800  
CTCCCAAAGT GATGGGATTA TAGGCATGAG CCACTGTGTG TGGCCTAGAT TACTTATAAT 181860  
ACCTGATAGA ATGTAAATGC TATGTAAACA GTTGTTATAC TGTATTGTTA AAAGACAGTA 181920  
ACAAGAAAAA AAATCTGTAC ATGTTCACTC CAGACAAATG GTTTTCTGTT TTTTTTTTTT 181980

FIG. 6.69



TTTTTAATA TTTTGGTCA GTGGTTGGTT GACTCCAGGA ATGCAGAACC CGCAGATATA 182040  
GAAGGTTGAT TATGCGTTCA GAGGCAGGGA ATACCATCTT GGGTTCCAGA AAGAAAATGA 182100  
TCAGCATTTT CTGTCATACT CTGGTAAAAA CAGATCTTTT GAATGGACAG GTGTATTAAA 182160  
CCCTGTGGAG CTGGCTGGGC CTGGCGGCTC ACGCCTGTAA TCCCAGCACT TTGGGAGGCT 182220  
GAGGCAGGTG GATCACGAGG TCAGGAGTTC GAGACCAGCC TGGCCAATAT GGTGAAACCC 182280  
CAACTCTACT AAAAATACAA AAATTAGCCG GGCCTGATGA CGCATGCCTG TAGTCCCAGC 182340  
TACTCGGGAG GCTGAGGCAG AAGAATCGCT TGAACCCTGG AGGTGGAGGT TGCAGTGAGC 182400  
CGAGATCACG CCACTGCACT CCAGCCTGGG CAACAGAGTG AGACTCCGTA TCTAAAAAAA 182460  
AAAAACAAAA ACCTGTGGAG CTGATGAAAT CCTGCAGGGA GCTTCACGGT GACAGCAAGA 182520  
GGAGAAACAC ATCCCCATAT GCCCCGCAGA GTTTGAAGTC CCGGCTGCAC CTCTCCCCAG 182580  
CAGCAGGTTG ACTCTGAAA GTTGCAGCGT TCTTACCTAC AGAGTGGGAA CAGTACTACC 182640  
CATTGCACAG AGTGGGTGCA AAGCTCTGTG ACGGAATACA TGGCAAGTGC CCACCACATT 182700  
GCCTGGGATG AGGTGGGCCC TTCCTTACG TAAGAGAGCC CTACAGATAC ACTCAAAGTG 182760  
GGCACATTCC TACAGAAGGA GTGTTATTTG TGTAGAAAAG AAAACATGA AAGGCTTTTA 182820  
TTCCTATACA CAATAAAGCA CCCCTTTAAT GTCTTTTGA GGAGGATAAT ATGAAATTGA 182880  
TGAAAAGGAA CCCTGTGGTT GGATCCCTGA CAATCACATG TATCCCTTTT TCACTCTTG 182940  
AAAAAGGAGT AAAGGAATAA AATAGAAGGG GAGAGGGGGC AGAGAGACCT TCACCGCCCC 183000  
CCCCCACCC CCCATCATCC AATCTATAGT CAAACCTCC AGACTGTGTC TCCTTGGCAT 183060  
CTCTGACACC CCCACCGCCA CCACCCAGT CAATTCCTAT CTTATCCCCC TATCCTGGAT 183120  
CTGATTCTGC TAAGTTCCTG CCACACTAAA GACAGGGTGG CTTTCTGATG ACAACATTCC 183180  
TCTGCTTAAA CCTGTCAGTA ATTCCTTGT GCTCTCAGAC GGAAGTAAGT TCTGAATTC 183240  
TTCACACGGC TCTCAGCAAG GTCACAGTCA CCCTGCTAGG CCCCAGGGGC AAATCTCAAT 183300  
GGTCATCTTC TTGAAGACCT GGCTCAGTTA TTTCTTTCTC ATTGAGGCTC ACGACCCAC 183360  
CTTCTTGCAT GCCTCAAACG GCCCCTTACC ATGCTCTTCT TTCGCCATA GCTCAGCACA 183420  
CCATATCATT TTAATTTATG TATTTTGCTT AATGTGGATG ATCTGTCTCC TCCTCTGCTG 183480  
TCCTCACCAG AGCATCAGTT CCTCAAACCA AGGCTCTTTG TTTTGTCTT GGATGCAAGC 183540  
TAAATGTCTG GCATGTGGCA AATGGTCATA GATACATGTC ATTGAAAGAA TGATTATCA 183600  
CCTCCCTCTT TGGCCTTGTC TGTGGTTCTA CCAATCCCA TTCCCTCCCC AGTGCCCTCC 183660  
ATTCCCCCTC CTTGGCTGAA CATTCTGAAC CACAGACAGT TCTTACCCT GAACCTTTGC 183720  
ATATTTTGTT CTCTTAGCTT AGAGCGGCCC CTCTCCCTCC GTCTGCTTGG CTAATTTCTA 183780  
CTTGTTCTTC AGATTTTATC TTAGATGTCA TTCCCTCAAG GAATCCTTCT GTGACTCAAC 183840  
ATGGAATTAA GTTGCCCTCT TTGACCCTGA AAGCACCATG TACTCAATCT CATCTTGGCA 183900  
TGACTCACTT TGCTGTGTGG AATGTCTGCT TTCCTTGTTT GTCTATTCCT TTAGACTGTA 183960  
AGATCCTAGA AAGTGGGGGC CGTGCCTTGC TCATGACTGT GTTTCTAACA CCAAACACAG 184020  
TGTTCAGTAG AGAGCAGCTG CTGAGTACGT TTCTGCTAAA TGACAGTTGA TGGAGGACAT 184080  
TTAGGGTTGC TTGGAGGTCA AGTCAAGGAG GCATTTAACA TTCTAGTAAA ACAAGGAAGT 184140  
AACAGGCTCC TGAACATGCC CACAATGAAC CAGATGCAAA CCTTTTCCCT TGGCAGGATT 184200  
CTTTGCCCAT AAAGTGGAGC ACGAAAGCAG GACCCAGAAT GGGAGGAGCT TCCAGAGGAC 184260  
CGGAACACTT GCCTTTGAGC GGGTCTACAC TGCCAAGTGA GTCCTAACCC TGATGTTGCT 184320  
AATAAGTGGG GGCATGGGCA GGGGGGCCTC CTTCTAGGAG TGATGACCAC CCTTAATACC 184380  
ACATGTCTGT CTGAGCCAAG TTTCTGAGCG CCAGGGAGGT GAGGAAGGTT GGACTTCACC 184440  
AGAGAGGCTT TGTGGACACC CTTTATCATC TTAGTGAGTG CTAGTGTCAA AACAAAGGGA 184500  
GTGGGGATAT GGGGCACATT GGTGGAGGGA GGTGTGATCT CTGCAGCTTC AGAAAGATCT 184560  
GAAAGAGTCA TTTGGTTAGA GAAGTTGACC TATTCCTGT GGGGTTAGAC CAGGTTGCT 184620

FIG. 6.70

ACTGTGAACA CCAGCCATGA CTCACCAGTC ACCTTCAGAA GCCACAGGCA GGACATGCTG 184680  
ACGACAGCCT TCAACTCACC CACCCCTTGC TCCCCTGCGG GTGGAAGTCT GGAGGTGACA 184740  
CCACTGCATT TTCTAACACG GGGGCTCCTT GAGCAACTAG AACAAGAACA GAAAGAATGG 184800  
GGACATTAGC AGGTGCTTTC CCCCTCTCTC ATTCTTTTCT TTGAATAAAA AGGTTGTTTG 184860  
AAAACACCTG AGCGGCTCCT AAAGATGGGT GCAATCTATT CGGGATGCAA ATCCGAATGA 184920  
ATGTTATTCA AATGCTCCTC TCTTCTTTAT GCAGAGTGTA TTTCAAGGCT CAGCCAGTGG 184980  
CAGGCATGCT GGGGACTATG GACTACGGAC TAGGGGCCTG TCACAGAGGA AGGCCTCATG 185040  
CTAGAGAGCT AAGGGAGGAG CTGGCCTTCA GTTCCATCCC AGGAGCAACT TTGATGTTCC 185100  
CAGAGATCCT TCCAAAGGGG GAGTCATGGT CACCCAAGAA AAATGTATTC AGAATGCCAA 185160  
GAATGGTGCA AACTCAGGAC AAAGATTAC ACTGCAGGGT TGGAGTCCCT GGGCTTGCTG 185220  
CTGGCACCAT GGGAGGGAGG GTCCCTTCA GGGGTACCGT TGGTTTCCTG TGAATTAAC 185280  
TGGCTTCAAG GGATCTCGAC TGAACAGGCC TATATCACAC TCACTGATAT ACTCTCTCTT 185340  
CAGTCCTTCT CCTCATCTAG GTATTTTAA TTGTTTCAGT GAGGTGTAGG CATGAGGGGA 185400  
TTGGAGGGGG CATCTCCTCC ATTGCAGTTT TTCATTGGCT GCTTTGCTCC CTCAGCTCCG 185460  
AAATCGCTGG GCCACTCTCG AACGCATTAG TACGGTAGTC ACAGGTTGAT TGCCTGGCCC 185520  
CTTGCCCTCT GTGGGCATTT TCCCTTTCAG ACAGCCCCTG AGTACTCACA GTGCTGCTAC 185580  
AGTGGGCCAC CTAGATCTCC CTCTTCTCC ATGCTCCAC GTGCTCTGGG CTCCACTCCC 185640  
TTCTCCAAG CACTTCTGTC CAGGGCTATT CCAGCAGTCT GACCTCAAGG AAATCCTTTG 185700  
CTAACTGAT TATAGAGAGG TTTCTATTTT AACATTTAGG TCTTCCATGT ATTAATTCTC 185760  
AGAATCAATT TAAGATGTTT AAAGGTGTGA TTTAAGACAT TTTAAAACCA TTTGGAGGAG 185820  
AGTACAGAAA TTATGTCACT TGCTGTCAGC CTCTTTCAC CATCTGCAGA GAAAGATACT 185880  
AGAGTCCCGC CTTGGACACA TCCACATGCA AGAGGTGCAA AGAAGGTGTC TTTGATGAGG 185940  
CAAGGTCAAA ACTTCTCCCC AGACGAAATC CAAAGAAAGC ATTCCTACTA TGCTATATCA 186000  
GTTTGGAAG AAAAATTCT GCCAGGTGAC TGCATTCTCA CTGGTCACAT TGTGTTCTA 186060  
TGGACTCCTC AGCTCAACCA ATTTGGAGAA GTTATGGTGC AATTCACCA TATCTGGTTA 186120  
GAAGTTAAGT TTCCAATTTG CTGGCAATGA AGAAGAAATG GAGCAGGCCA GGCTGTGTAG 186180  
TTTCTGCCAC GTGCCCCCGG GAGTGAACAG CTCTGTTTGT AAGAAGCCAT GGTGCTTAGA 186240  
CCTGGGCTCG CTAGTTGCCA GCCTCCAAAT TGCAGAAAGT CCCTTTGGTT GGTGGCTATG 186300  
CTGTGTCACT TGGGAAGGTG GTTTGGAAGT TCCACAGTCG TTGTGGGGTG CCAGAGATTA 186360  
AAAAGCGTAA GAGGAGAGTG GAAAGTGATT GTTGCTGCTT GGGCATCCCC ACGTGTGGG 186420  
TGCTGCAGCC CAGCTCTCAA AACCCATGGG TCTGTACACT CAACCTCCAT GAGAGGGAAG 186480  
GAGAAGGATG AGGGAGGGGA GAGATAGCCA TGGAAAGGTA GGAAC TAAGC AGGCAGGGTG 186540  
GAGAGTTTTT TGTAAGACAA AAAGTGTCTG GACACTGCTG CGGTTCTGTT ACAAAGACCA 186600  
CTTCTCCCT GGGCCAGCAA CATATCTGTG TGCCTGTCTG GGTTGTAAAA AGGGTCAAAG 186660  
ATCAATGCAG CAGGCAGCTA CATGCTGGCA AAAGCCAGAG GCAGCTGGTC TGTTTGCCTG 186720  
TGCCAGGAAA CCACTGGGAA TGGGGTTGTG TGTTATTCTA GGAGAAAGTC GTCCCAGCAG 186780  
CAGCTTCTCC AGGGGCATCC AAGAGCACTG AAAAGGGTTG CAAGATGACC CATGAGGCTG 186840  
CAGGAAGAAA AGAACATGCA TTTAATCTTG CTATCTGAAA AGTAAGACAT GAAGCTTTCC 186900  
TCATTTTAA TATACACATG GACAGTAGTA TGTGTATATA GTTTATATGC AAATATACTT 186960  
GTTATAAGGT TGCATGCTCA AAATTTTTGG TTCATGGGGT GTGGGATCAT AAATGTTTAG 187020  
GGACCATGGC TATCAAGGAA AACAGCATG AAGGATAAAT GATACTGGTG GATTAAAAAG 187080  
ACAGATGCAT GTATTTT TAG CATAAAACAC AACTGCTGAC TGATACAGAT AGCTCAAGAT 187140  
TCTGGGGCAG CTGCTGAACA GATACACTAG CCAGTGTGGC TCATCGGCTC AGACTTGGCC 187200  
TTAATTAATG GGCTGTCCCT CCACCCATCT CCCATGAGGG CAGAGCTGAG CCAGGGTTTG 187260

FIG. 6.71

AGAGCTAAAA GGAATTGGAC CTGGACTCTG TTCACGTGTA TATTTTAATT CTAATTAATT 187320  
CATTCTTTTG AAAGACAGAG TCACACTCTG TTGCCTAGGC TGGAGTGCAG TGGCACGATC 187380  
TTGGCTCACT GCAACCTCGG CCTCCCAGGT TCAAGTTATT CTCCTGCTTC AGCCTCCTGA 187440  
GTAGCTGGGA TTATAGGCAC ATGCCCCCAT GCCTGACTAA TTTTGTATT TTTAGTAGAG 187500  
ACGGGGTTTC ACCATGTCAG GCTGGTCTTG AACTCCTGAC CTCAGGTTAT CCACCCGCCT 187560  
TGGCCCCCTCA AAGTGTGGA ATTACAGGTG TGAGCCACCG TGCCTGGCCT GTTCACATGT 187620  
ATAAACACA GTTTAATGTC CTATTCCCAG CCAATGAGCA TGGCTAGAGC AGCCTTGGTC 187680  
AAAGTTTGGT TTTTGGAGAA AAATCCTTGT TAGCTGACCT AAGATTCTC TTTGTGAGTG 187740  
TAAGTAAGCA CAGGTTGCAG AGAGGAGAAG GGTCTCTGGA GAGGTGTAAT TTTCTAAATG 187800  
GATTACAAGT TCATGGACTT TTAACAGGTG TTACAGGGGA TAACAAGTTC TTTATAGACA 187860  
GACTTTTGAG GACGTTTAAG GGTATTCTGA TTCTTGGTTT TCTAAGAGGG GAATGTATTA 187920  
TTTAACTACA GACACCCCTA CCGOCCACTT TTTGCAGAGT GTATCAAAAC ATGTTTTTGG 187980  
AATACCACCC TCATGTCGCT TCTCCCTGCA TCTCTTATCT CTTGGTGTCC ATTCTAGACT 188040  
CACTTTCTTT CTGTTTTTTA TTTTATTTT TTTTGTAGAT GGAGCTTCAC TCTGTCACCA 188100  
GGCTGGAGTG CAGTGGTGCA ATCTTGGCTG ACTGCAACCT CTGCCTTCCG GGCTTAAGCA 188160  
ATTTTGTGC CTCAGCCTCC TGAGTAGCTG GGATTACAGC ATGCACCACC ATGTCCGGCT 188220  
AATTTTGTG TCTTTAGTAG AGACAGGGTT TCACTATGCT GGCCAGCCTG GTCTCAAAC 188280  
CCTTACCTCA GGTGATCTGC CCGCCTCGGC CTCOCAGAGT GCTCAGATTA CAGACGTGAG 188340  
CCACTGGTGC CTGGCCTAGA CTCACTTTCA AGTGGCATAG ACTTGTAATAA TTATTTAAAG 188400  
GTGATAGGTC TACAATGATC CTGTCAATTA GTATTGACAC TATTATTAAT AAAGTGTAT 188460  
TAATTATATT TACTACTTT AAATTAATCC AAATAATTA ACGGAACACT AAAGAGTTTC 188520  
TATGTTTTAT TCCCAGAGGT GGAGAAAAAT GAAAGGGAAT ATAGCAACGA ATTCTTTTCT 188580  
CCATAAAAAC ATGAATAGTG CAGCACATCA AGTTGAACAT ACCACAGCAA ATTGTTGCAA 188640  
GATCTGCTGA GTAGCTCCTA TTAGACCTC AAGGAATGAG ACTCAAAATG GGTTCATCAG 188700  
TTCTGTTTTG CAGAAAAAAT AGCGCAAAAT TTCTCAAAAG AAAATCCAGA ATAATAATAA 188760  
TTTGTCAATA GGAAAGACAT TTCCACTGGG GGTTAAGAAG GAAGACATTG GAACAATGAT 188820  
AGCCACCACT TATTGAATGC TTAAGTGAG CCAGGTGGCA CTTACCTTG TTTATTCTC 188880  
ACAACAGTCT AGGGAAGTAA TTAATAATGT CTCCATCCAC CTCTTGTA TAGACAACT 188940  
GAGGCTCATT GAGGCTAGGA AATGCACCCA CACTCACATA GCCCATAAGA GGCAGCCATG 189000  
GCATTGGGCC CAGACCATGT GAACTTCAAA GACTACACGA GCAGCCACTG GGCAGCTGTC 189060  
ATGGCTAAAG CCACTTGAAT TCAGCCCAGC AGCAACCCCT TCTCCAGGAG GGGCACATAA 189120  
GCTTGACAGT TTGGGTAGAA GCTGCACTTG AAGTCTGGA TGGCGAGAGG GACTGGCTTG 189180  
AGCCAGAGCC AGGAACAAGG CTCTGAGAAT ATTCTGAAA TCCACAGGAG GAACCCATTT 189240  
TCTTACAGCT GGGAGAATTT CATTCAACTC CAGGCTGACC ATGTTTTATT AGGAACGAAG 189300  
GTGACTTGAA CTAATAGTCA GGAATGGTTG AATACGGACC CAATGTCAA TCACTAGGCA 189360  
GTTACATTT CTAATGAGCA AATCCCTTAG ACAATTAAGA ATTTTTTCC TTTTGCATAA 189420  
CCCAGACAAA ATCGCTACTT AAAACAAAC CAAAGACCCG AAACATGAGA AAGAGAAGGA 189480  
AGCAGGGGAA ATCTTTGGTA CTAATAAGTT TTTAAACAAT AAGAGCACCA GATATTTTAC 189540  
CCCATCAGAC ACAGAATGTT ATTCGAATAA CCAAAAAAGG AATTTTCTCT CTAAGTTTCT 189600  
TGAAGTGAA AATGAATCAT ATTTTCTCAG TCCTGAGGCT GCAATTTTGT GCCTCTAGTA 189660  
ACATATAAGA ATAGATGTGA TGCCAGTGCC CAGTAGCTGC TGCAATTGTT ACTTGGGGAC 189720  
CTGTTTATTC ACTAAGCACT TCACCCAGT GATAAATTTG TAGGGGCCTC CTGCCCTTG 189780  
GAGCTCCTAC CGTGTCCATT AGATCAGTGG AAATCTGGG ATTCAGAGCA CTTTGCAAGG 189840  
TCAGCAGGGG TCTGCTCTTT CTGTCCTGTT CTGGTGTGTT GGTGTGCCT GGATTCCAGG 189900

FIG. 6.72

GTAGGTTTCT CATCTGTTAC CTTCATAGAC TTCTCCAGAA AAGGATCTTT TGACCATCAG 189960  
AGGACCACGA AGATTCCATT GGTGAGGCGC AGATAACCTG ATCTCTCTGG GTTCTCTGCA 190020  
GGGCACAGAT GAAGGGCTGG CCATTCCCAA GTTCTCAGTG GTACCACTGA GGCATGAGAC 190080  
CCTAATGGTT TGCATGAGCA GTTTGAAAAT TGCATCTTTG TTTTACCTA TATAATCACA 190140  
TGAAACCCGT GGTCTCAAA CGTCAGCAGG CATCAGCATC ACATGGAGGG CTTGTTAAAA 190200  
CAGATTTCTG GGCCCAACA CAGAGTTTTA AATTCTGAAG GCCTGAGGTG GGTGTGAACA 190260  
TTTGCAATTC TAACATGTTT TCGATGCTGC TGCCGCCTCT GGTCCCGAGA GCATGCCTGG 190320  
AGAACTGCCA CCTTCGACCA TGGACTGTGA GAATTCACAT GGACCTCAGA ATTATAATCA 190380  
GTCTCTCAGT TTTACAGATA AGGAACTAA ATCCAGAGAG ATTGTTTTGC CAATGGTGAA 190440  
CAGCTGGTTA AAGTCAGGAT GGAGACTTTA ATCCTAGTCA AGTGACCTTT CCTCTGTATT 190500  
TATTTCCCTC CCTTTTATG CCTCTCAAGT CTAGTTACAC TGTTTTTCAT GGATGGGCAT 190560  
ATTTATTGTC CTGATCTGGA CTGCAGACTT CTCAGGAGGA CACCTATGAT TTAATTTAGT 190620  
ATAGTTGAAG AGTTAACAGA CATGGCTTTG GAGACAGACT GATTATGGTG TGAATCCCGG 190680  
CTTTGCCACT CCCTAGCTGG ATGACCCTGA GCAAGTTATT CAGCTTCTCC AAGCCTGAGT 190740  
TCCTTATTGG AAACATGAGA GCAATTGTGA TAGGCAGAAT AATGGCCCCC TCACCAATCA 190800  
TGCCACATC CTAATCCTAG GAACCTGTGA ATATGTTATG TTACATGGCA AGGGGAAATT 190860  
CAGGCAGCTA GCCAGTTGGC CTTAAATAA AGAGATTATC CTGGATGATC TGGGTAGGAC 190920  
CTGATGTAAC CACAAGGGTC TTTTAAATGT GGAAGAAGGA GGCATAAGAG TAGATGTCAG 190980  
AGTCATTCAA AATAAGAAAG ATTTGATGGG CCATCCCTGA CTTTCAGGTT GGAAGGAGGT 191040  
TCTGAGTCAA GGAATACAGG TGACCTCTAG AAGCTGGAGA AGGCAAGGAA ATGTTTTCTC 191100  
CCCTAGAAGT TCCAGAAGGA TTGCAGCCCT GCTAATATCT TGACTTTATA GCCCTTTGAG 191160  
ATTTATTTTG GATTTCTGAC ATCCTGAACC ATAGTAAAAG GGTGTTTTTT GTTTTTTTGA 191220  
GACAGAGTCT TGCTCTGTTG CCTGGGCTGG AGTGCACTGG TGTGATCTTG GCTCGCTGCA 191280  
ACCTCCGCCT CCCAGGTTCA AGTGATTCTC CTGCCTCAGC CTCCTGAGTA GCTGGGATTA 191340  
CAGGTGCTTG CCACCACACC TGGCTATTTT TTGTGTTTT AGTAGAGACA GGGTTTCACC 191400  
ATGTTGGCCA GGCTGGTCTT GAACTCCTGA CCTTGTGATC TGCCTGCCTC AGCCTCCCAA 191460  
ATTGCTGGGA TTACAAGGCG TGTTGTTTTA AGCCACTCAG TTTGTGGCCA CTTGTTACAG 191520  
CAGCAAGAGG AAATCATAC AGTTATCATG TGAATCACA GGAATATGGT GAGTTAAAAA 191580  
GAGAGGAAGG GTGCAAAACA TCCACGGTAG AGTGAGAACT CTCCAGGGAG TGAGGACTGT 191640  
GCCCAGCATA CAGTGATCAC CCTCTTAGTA AGCTAAGTTT CTGAGCACCA GCTTTTTTGA 191700  
GTTGACTTTG TTGTCTTTAA CATTTGAAGA TCACCTTCTT TTGCTCAGCC TGGCTTGCA 191760  
ACCTGGGCTG ATTTGTGGAT CTGATAGAAA AGTTTCTTA GTTGGGCTCT TCTCCCCGAC 191820  
CACCCCCATG CCAGTGTGGC CACATCCTCT GTCTGCATTG CTCACTCTTC AATTCCAAGA 191880  
AGCGCAGGGG CACCGCCAGG AACAGGAACC CTGCCAGAGG AATACATCAA GAAACCAAGT 191940  
CTCCCTTACG CATCACCCTA GGAACAGAGT TAATGGATTA TGAACATGTG TTTGCTTTAT 192000  
ACCATGTTT GTTTCCAGG TGGCAGCTGG CTGCCCCATC TTATTGGGTA GATGTAAGTG 192060  
GAATTACGAA TGGGATTTAT GTTTCATGCA CGATGGTGAT TATTAATTC AACTTTCAGG 192120  
TAATTTTCAG ACCACATTGC ACTAATTGG TCTCTGATTG TTTTCTCCT TGTTTGTTA 192180  
TTCTGCAGCC AGAACTGTGT AGATGCGTAC CCCACTTTCC TCGCTGTGCT CTGGTCTGCG 192240  
GGGCTACTTT GCAGCCAAGG TAACTCAGAC TTCCCTTTGT TCATTCTCCT TCTATAAAGT 192300  
GCATCTCAAG GAGGTTCAAA GGGCAGGCTT TTTGTTGAAA GGAATTTGCC TGACCTCTGG 192360  
CTCCCATCTG TGAAGCCCTG GAGAGGTGAG AGCCCTCGGG AGGCCGTGTT TCAGGCATGC 192420  
TCTGCACCCG TGCAGAGCGC GTGTGATAAT GCATTGCTAA TGCTTGCTCC CTGGTGGCTG 192480  
GCTGAGAGCT GCTGTGCTGA CAAGGGTGGT TTAAGGCTAA ATGTGACTCA GAATCCTTAA 192540

FIG. 6.73

GCAGTGTTAG TTCAGATACA AGGGCATTAT AAATGAGAGT GCCTGAGGGA TCTATTTTGG 192600  
GACCGCTGTC ACTTGGCTCT TCTGCTAATA AGCTTCCAGT GTGGTGGCCC TCCTTCAGGC 192660  
ATGTTTCCAC TGAGCCACGG GCTGGATGCC ACATCCCCGG CCTTCCCACA GTTATCAGCA 192720  
GCCCACAGGC TTGACTTGAG CAAGTTGGAA AGACAAATCA ACTTCCAGAG TTGATTAAAC 192780  
ATTGAGTGGA AATCAGTCAT ACTTTTGGTC CCCTTTCGGG GCCACGCCTG GCACTGTGCC 192840  
TGGTGGCAGA TCGGCATGAA CTGGCCAGCT TCTGTGGCCC TGGAGGGCAC AGGCAGAAAG 192900  
GCCACACTCA GTCCCATGAT GAACTGTTTA AGACTTATTG TTGTCTCCCC GCTCTGTAAA 192960  
GTAGATAGAG TGGATTTTAT GTCCCTTATT ACCTTTCAGG ATACTTTGAC TCAGGGAGAT 193020  
AAAGTAACTT GGGTACAGCT ACTCAGCTGG TGAAGAACAC AGGCAGAATG AGTGCCTGGG 193080  
TCTTTTGA CT TAAAATTCTG GATTTTTCAC AAAGATCCTC TTA CTTTATT CATTTACATA 193140  
ATAAATATAT ATTGAAGAGC TACTCTGTGC CAAGCCCTGT GCCTAGATAT ACAGTGATAA 193200  
ATAAAGAGTA GCTTCTAGAG GTCACCTGGC GGTGAGGCAC AGGCCAGCTG GCAAGATGGA 193260  
CCACAGAAGT CAGTGAATGA AGACAATGAC AAGGGTGGGA AGCGCCATAT GGAAGAGAA 193320  
CCAAGTTCAG TGATAGAGAG CAGAGGTGAG GCGGCAGCAG AAACCACTTA AGGGACACCA 193380  
CGTGGCACTC CTTCTGTGCT GAGAAGGCTG TCAGTAAGCT CACCATTAT TTTCTATTTT 193440  
CTCTCCTGAG TTAAATAGGA AACATGTCTC GCATTACTTG AAAAATCAAG TCAAACTATG 193500  
CTCTTACTAG GAGTTATGGT TCTTTTATG TCTTAGATGA TGCTTGATCT AGATGAATGC 193560  
GGACTTGCTG TAGCTAGATA AATACAATGG GAGTTTGAAG GTGTTTCGTA GCCCTGGA 193620  
TAGGTATTTT CTGTCAAAAC AAGCTTTGTC ATTGCCAGCA GACAAAAGCA TCAGTAACCT 193680  
TGGTTGATAA TCGTCATTTT TTAGGAATAA AGTAGACTGT AGAATTTTTT TTAGCAGAAA 193740  
GGAAACCCAA AGATAATTCT AGTGCAAATC CCTCACTTTA TAGAGCAGAA GCTCAAGTCC 193800  
CAGAGGAACA AGTGGCTTGA ACGAACATCA GAATTTTAGG GGCTGGATTT GTACCTCCT 193860  
GGTGCCAGCA GCCCACTTCC CTGCAGGAGG CACTCACCTT CTTGCACAG GGGTATGAGT 193920  
GTGGCCATTT TCCACCCATA ATCTCTGTGA GCTCATGTTT AATTGGGTTT CCATTGAAAG 193980  
AAAAATGGAC CAGTAAGTTG GAGCAGAATC ATTCAGATGG TATAACATAA GGAAAACTT 194040  
TGCCCAAGGC AAATCGTGAT TGTGACAGCT TTGTGATTTT TAGAGAATAG CATGGGCCAG 194100  
GCACAGTGGC TCATGCCTGT AATCCCAGCA CTTTGGGAGG CCGAGGCAGG CAGGTCACTT 194160  
GAGGTTGGA GTTCGACAAC AGCCTGACCA ACATGGAGAA ACCCTGTCTC TACTAAAAAT 194220  
ACAAAATTAG CTGGGCGTGG TGGTGATGC CTGTAATGCC AGCTACTCGG GAGGCTGAGG 194280  
CAGGAGAATC ACTTAAACCT GGGAGGCGGA GGTGCGGTG AACCAAGATA GCACCATTGC 194340  
ACTCCAGCCT GGGCAACAAG AGTGAACTC CGTCTCAAAA AGAGTTCACA GTTTCTCTTT 194400  
TGCTTTGATT TTCTTATCTG CCGGATAACA ATAGTATTTT GGAAGGCAGG AGGAATTGTG 194460  
GAAAGAAATG GGTTTTGGGG AGTGGCTGAT TGGAGGCAAA TCCAAGGACA CTCATTGCTG 194520  
GTGTGTGACT CCAGGCAGTT ACTCAGCTTT TCCAAGCCTC AGTTTCCTTA TTGTAAAACA 194580  
GGACCATGGT CTAGCTAGTA GCATTCTAT GGTGAGTGAA ATAATATGTA TAAAGCTCCT 194640  
GACACAGTGC TTGGCATATA TCAGATTGAG CCATGTAAAA CTGCCAATAT CTGGCTATTT 194700  
ATGACCTACA AAAATAGCAT TTCATATGAT TCCACCTAAC ATCTGAAGCG CAATAAATGT 194760  
TATTATTGAT AATGCAGGTG GTGGTGATAA AGTTTTGAAA TCAGAAAGAC CTGGCTTCAA 194820  
ATTCCACGCC TTCACTGGCC TGACTTATTT TCATTCATTT GACAAATATT ATTTTGAACA 194880  
CCCCATGTG CCAGGCACTA TGCCAGGCTC AGAGATGATC TAGGAAAAAG ACAGATGTCC 194940  
TCATCTGTCT TAGGCTCTTG TGGCCTAAGC CTAAATTTCC TCGTCTGTCA AATGGTGACA 195000  
GTAACACACT CCTTACCAGA GAGCTGGGAG GATTGGAGAC TCAAGTTCCC AAAACGCCAG 195060  
GAGCACTGCG GCAGGTGAAA AGTATTCCCT CAATGGCGGA AGTGTTTAAA TTGCTTTTAT 195120  
ATCTGTAGCT CTAGATAACA CTAGTTCCAG CTTAGTTAAC TCCCAGCTCC AAGCCTTCAG 195180

FIG. 6.74

GACTTCATAG AGTTATTGGG GTGCTGCTCT TGGCAGTTTC CCAAAAAGCT AGAATGCAGA 195240  
GGGAATCTCC TTCCCAAAAA GCTAGAATGC AGAGGGAATC TCCTTCCCAA AAGGCTAGAA 195300  
CGCAGAGGGA ATCTCCTTCC CAAAAGGCTA GAACGCAGAG GGAATCTCCT TCCCAAAAGG 195360  
CTAGAATGCA GAGGGAATGT CTTCTCTTC TAAATGGTAG CTGTTAGTTC AAGAAAGGTT 195420  
AAACATTGTG CTGTGGGGAG GCTCAGGGGT GAAGGGTGTA CTTTAAAGAG AACCAGTTTC 195480  
AGAGCTGGGT TTGGGGTTTA AGCCCTACCC TCTGCCCCCT TTTACGAGCT GACAGCCTTA 195540  
TGCAAGCCTG GTTGACCACC TGAACCCACG TTTCCACATC TGGAAATAGA AATGTGGGTA 195600  
CTAGTTATGT TGAAAGGACT CAGGTTAGAT GATAGATATG CAAATACCTT GGAAACCAGG 195660  
AGTGTCAGT CTTTTGGGTT CCCTGAGCCA CACTGGAAGA AGAGTTGTCT TGGGCCACAC 195720  
ATAGAATACA CTAACCCTAT CAATAGCTGA TGAGCTAAAG AAAAAACGTT GCAAAAAAAA 195780  
TCTCATATTT TTAAGAAAGT TTATGAATTT GTGTTGGGCT GTATTCAAAG CCATCCTGGG 195840  
CCACGTGCGA CCCGCAGGCT CCGGGTTGGA CAAGTTTGTT GTAAACAATG CCATGATGCC 195900  
GGCATAAGGT CGTTACCAGT ATTAGGAAGG TTCTCAGGTT TCCTCTAGCC CTTGGGCTCT 195960  
TTTCCTGAAG TCGTGTGTC TTCTGCTAGA TTTGTGACC AATGTTGATT GCCTAATTGG 196020  
GCTAACAGCA TGTTTTGGTG GCTACGAAAC TGACACAGGT GTTTTCATTT CTCCACTTAG 196080  
TTCCTGCTGC GTTTGCTGGA CTGATGTACT TGTTTGTGAG GCAAAAGTAC TTTGTGGT 196140  
ACCTAGGAGA GAGAACGCAG AGGTAGGTAA CTGGGACTAC TAAAGAACTG TGGAGCGATT 196200  
CCTGATTTTT GAGCAGGAAG AGTGACAATT CAAACAGTA TTTGACTAGA TTCACGGCTC 196260  
CGTAGCATCC CTTGGGTGG GAGGGGGAAG GCTGACTAGG ACCTCTGATT CTTCTTTCCC 196320  
TGAGCTTTGA AGGCTCTGAA AATACAGCTG GGGGGACTTG CCCAGTTTTT TTATTAAGCA 196380  
ATTCTCCGC ATGGTGCTGG CTTTCAAAGG GTGCTTCAGT GCTGTTTGCT GCACGTGCCT 196440  
TGCAGCCCCA CACCCTGCAC TCCCGCCCTG CAGAGTCTGG CGCTGGAATG ACATTTTAGG 196500  
TCTGGGTTCC CAGGCCTCCT GAGAGTGAAA TGTTTCATTG TTTGTCTAGA GAAATGAGAA 196560  
CTAAAGCTTG CACCTTGTA TAAGTTGTCC TGAGGAACAT ATCTTTCAGG GACCAGAAGA 196620  
AAGAATGTTG GGAAAATAAG ATGCAGTAAG ATGCAGACAT GACAGCAGGG TGCAGCGGCT 196680  
CACGCCATA ATCCCAGCAC TTTGGGAGGC TGAGGTGGGT GGATCACCTG AGGTCAGGAG 196740  
TTTGAGACCA GCCTGGCCAA CATGGTGAAA CCCCCTCTCT ACTAAAAAAT ATACAAAACA 196800  
TTAGCCAGGC ATGGTGGTGG GCGCCTGTAA TCCCAGCTAC TCCATAGGCT GAGGCTGGAG 196860  
AATCGCTTGA ACCCAGGAGG CAGAGGTTGC AGTGAGCCGA GATTGCGCCA CTGCACTCCA 196920  
GCCTGGGCAA CAAAAGCAAA ACTCCATCTC AAAAAAAAAA AAAAAAAAAA AAAAAAGAT 196980  
GCAGACACGA GACTGTGAAA CTGACTAGCA TCACCATTGC ATTGTTTATA GATGTTGCCA 197040  
GACAGAAAGC CCCAAAGCAG CACAGTACCT TCCTGACATC TGGACTAGGA AATCTAGATT 197100  
TTAGTAAAT ACATGCTAAT ACTTACAGAA GAAATGTCGG CGTTAGAGTA TGCCGTCAGT 197160  
TCCTTAGAGA TTGCAATTCC TAATGCACTA GTATGGTTTC AGGTGCCAGG AACACGTTCT 197220  
GTGAGGCTGC TGCCCCAGGT GCTGACCCCA GCCTTCCACA CCATTTTCCT TCCTTGTTGT 197280  
CACAGCCGCT CTGTCTTTA CAATAGCACC CCTCTCTAGT GGCTAATGGG CTCTATGATT 197340  
AGATAGCATC CTTAGTAGT GATAAAGGCA GTGACATCCT AGGGAGGTCA GCGGGTGAAA 197400  
GCGCTATATC TGGA AACCT GAGAGCCTGT GAAGCTCAAG GACTTGACGG GGTTAGACCG 197460  
TGAGCCGGGC TGCAGCTGGA AAAAGAATGA CTGTTCTTTC AGCAGATCCT TCCCTGTGCC 197520  
ATCTCTTCT TCATTCCTCT CTAGTGGCAT TCTTATTTAT CCTCTAAAC CACAATTCCA 197580  
TTATCTCTCC TATTCCTATC AACACTGCCC TAAATGATAT TCTTATTCT CTTTGGCCCT 197640  
GGAAACCTC TATCATGCCT TTCCCATGT GATTACCTCG TTAAGAGTGG GGGTGGAAATG 197700  
TCTAGCAATG AAATAAGAGG GTCTTCTCTT TTGCCTGGCT CCCTATGCAG CCCTATCTTA 197760  
CCCCCTGCAA AGTCCCAGGG ATGTGGCTCA GTCAGTCTC CTCTCTTCAT CTGTCACCAC 197820

FIG. 6.75

TTGCTTGAGA TCCTACAGCT GCTTTAATTC CGAGACCATC TGCAGAACAT GACAAAATTT 197880  
GTCCACCTAC CCACATGTCC TTTAACTTT AAAGGCTTTA CTAAGTATT CCTATTAGGG 197940  
AATGAACAGA GGTGGCAAAA ATAACAATA GGAGATTGAT TTACAAGAAA TCTTTAAAT 198000  
AGTAGATTTT TCGGACCTC ATTGAAATAT AAATGGCCTG CTTCTTGTG TCCCTCCCTG 198060  
GTCTCCCTCT TTAGGTGATA AGAAGAAGAT CCTGCCAGCC CCATAACCCG CCATCTGCGC 198120  
GGGTCTAGA CCCCTTCTC CTCCCCTCTG GCCGTGGTAG GCATTACTGA TGAATCATGG 198180  
TGCTCTTTCT TCCAGAGACC AAACCTGGCC TCGGAATCCT TCTTAACACA GATACTGCTT 198240  
AACACAACCA CTCTGAGCAG CTGTCATAAG TAGAAGTAAT AGATACTAGA AGAAATGTCT 198300  
AAGCCTAATC TAGACCAAAA TACGGCCTGA TATAGATGCA AGCCAGAGGG GCTTTATGGT 198360  
TAAATGCAAG GAGATTTTCA ACCCTGCCGT CTAGAAGCTA CTTGCTGAGA TCTTCTCAG 198420  
TTGGGCCCCAT CTCCTCCCCA GGCCTCTCTT CTGTTCCCTGG GCTATGTCAC ACTTGGACTC 198480  
TGCAGACACC TAATGCTCTT GGGACCTGCT TTAGTTCTTG ACCTACCAA CCGAGGAGGA 198540  
ATTGCTAGAT GAGATCCTTC CCCCGGAATT TCTCTCTTGA ACCCCAGATG GTCCGTTGCC 198600  
CCTTTCCAGA AGTTGCTCCA GCCCTGTCCG CTTAGGAAGT TCAGTGTCTC CTTGATCCA 198660  
GTGGGTAGGG AAGACATTCC ATAATGAATG CCCAGTCTG AGCTTCTTCC TTCAGGCTTC 198720  
AGGCTGCCCT GCGAGGATTT TGCAGCTCCC TTTTAAATGC CCTCTAGAAG TTTCTGGCTC 198780  
TTATTTTCTCAG CCTTCATCC TACTCTCTCT GACCCCTTCC TCTATCCTGT TTAGTTCACC 198840  
TGTAGCAGTT ACTACCCAGC AGTGAAGGAT GAATCTTGGT TTCGTTTCTT TTCTCTTCTT 198900  
TTCTTTTTTC TCTTCTCTT TCCCCTTCCC TTCCCCTCCC TCCCTTCACA TCACCTCATC 198960  
TCACCTCACC TTACATAGTC TTGCTCTGTC ACCCAAAGT GAGTGCAGTG GCCTGATCTT 199020  
GGCTCACTGC AACCTCCACC TCTTCCCAGG TTCAAGTATG TCTTATACCT CAGCCTCTTG 199080  
AGTAGCTGAG ACTACAGGTG TGCACCTACCA CACCCAGCTA ATTTTTGTG TTTTAGTAG 199140  
AGATAGGGTT TAGCTATGTT GGCCAGGCTG GTCTCGAAGT GCTGAAGTCA AGCAATCTGC 199200  
CATCCCCGGC CTCCCAAAGT ACTGGGAGTA TAGGCATAAG CCACCCATGA TGCCAGCCT 199260  
GAATCTTGGT TTCTTCCCCA TTCATTTAAG CTATTACCTG GGCCTGAAGT CAATGGCACC 199320  
TGGCACCAAC TGGCAAGTGA CTCTTGGTCT TTTATTACCT ACCTTCCCTA GCAGGCACTG 199380  
GGTTGCTCCC TCTTCTATC CCATGGAGTC CTGTCCTCTG TTGGGGCTCC TACTGATCCT 199440  
CTTGGAATA TGAAGTTCTC AGCTCAATGG TGGGTGGGCA ATGACTGCCA ACTCTTGAGG 199500  
CCAATGAAGT CAGGTTACCC CACTCCTCTC CCTCTGAGT TGCTCACTCA CTCCTCATTC 199560  
ACTCAACATT GATTCAGTAG ATATTTGCTA CCTGCTCTGT GCCAGGTACC AGGTCAGTTG 199620  
CTGAAGGAGT AACAGTGAAC ATGACGGAGT CTTTGTCCCC AAGGAGACCC AAGGTGTCTC 199680  
CTAGAGCCAG GGGCACATTG CAAGACCAA TATATTCAAC TTACCAAAT AATCATAGAC 199740  
CTAGTTCTCA AAAAGCAAGA AGACTGATTC CTCGTTGTCA TTTCTCCTCC TCAGCATCAA 199800  
TGTTTTAGAG TCTGTGGGCC CCTCCAAGT TGGAGTATGG TGTTACTTCA CCAGAGTTTG 199860  
AGGAGAAACA TTCTTCTTTT GGAAGGCCGG GGAGCATAGA TGGATATCAA GGCTGCTGTT 199920  
TCTAAAAGCG AAACCCACCA AACAACAGTA TTAGAATCAT CTGTGGTGCT TATTAAGAT 199980  
ACAGATTCTT GGGCCCCATC CCAGACTTAT GAATCAGAAT CTCTGCCAGA GGAAGCCTGA 200040  
GAATTTGCAT TCTCAGATGA TTCTGCATTC TCAGATAACA CATTCTTTAG GTGATTCTTA 200100  
CACACACTGG AGTTTGGGAA TCGCTGAAGG CTGTTCACTT CTCTTTTCTG AGAAATGATT 200160  
CATTCAATTC AGAAATATTT GCAGAGGTCC TTATTTATTG GAGATTTGTG GGTGGGCAGA 200220  
GGAGAAATAT CTTGTCCTCA CAGAGCTTAC AATTTTATT TTCTTTAGAG GTCACCAGGC 200280  
TTAAATGAC ACTTCCCTAA ATTCTGAAAA GAACAGATTT TTAACAAG AAGGGACTGT 200340  
AATGTTTTCT GTTCTACCT CGTATTTTGT TCACATTAAG AACCTGGGGT GGAAGTGGA 200400  
GGAGGGGGGG TGAAGGGGGG GGGGCCACAG AGAGCTGAGC TGGGGTGGTC TCGAACTCCT 200460

FIG. 6.76

GAACTCAAGC AATCTGCCAG CCTCAGTCTC CCAAAGTGCT GGGATTATAG GCATGAGCCA 200520  
CCCACGATGC CTGGGTGGAA CTCAGGGCTC TGGATGCCTG GGCGCCCCCA TCTCCCACAC 200580  
TACGGCGCCT CATCCTAGAA GTGGTTAGCA CCTTTGAGAT GGGGAATTATT TAGCAGGATG 200640  
CTTTTGTGTT TTCATGTAAG TTTTATGCTG CCTGTGGAGG GCACAGCTGT TTCAAACTA 200700  
ATAACCAAAT CCTGGTCTCC GAAGTCTGAA GGCATCCTTT GCCCTGCAGT GCAAAGCACG 200760  
GGATTCTGGC CTCACACAGG CAGGTCTGAA CTCCTGTGTT GCCTCTTGCT GGCTGTGGGA 200820  
CCTGAGGCAA ATCATGCAAC CTCTCTTTTC TGTTTGCCTA GATGAAAAAT AGGTTTACAA 200880  
TACGCCCCCA TAGGATGGCT GTGAGAATTA AAGGAAGTCA TGGGTGTACA ATACCTGGCC 200940  
CCGAAAGATG CTTAATAATT TAATTCTGAC CTTCCTCACT CATTTAGGAT TATGTACCAA 201000  
CTTTTAGAAA CAATGAAAGA TTAGTGAGTC TTCTGTGGTT GGTATAAAAA AAAAATAGAA 201060  
ACATGAAAGA GATGTCCTCC TTGTTCAAGG GCTAATGACC CTGGTGTGCG CTGTCTAGGC 201120  
CCCCAAGGTC TTCCTTCCCT GCTCACAGCA TTTCAGGTTT TCCGCAGCTT TGCTGAGCCT 201180  
GGGTCAGGTT CGGTATCTGC CCACCATGCT CACTTGCCAC AGCTGTGGCC CCATTTCCAA 201240  
ACTTCAGAGA CTAAAGGTG CAGCTAATGA TGTGCCCGGC CTGGGGTCAC ATTCCTGAG 201300  
CCCTGCAGAC AAGGGAGCAG GAGGCTGAGC TCTTATCTTC CACACCCTGT GCACAGCCTG 201360  
GGAAGAGTTA AAGCACCTA GTCCTATGCT GCGAGGGCCA CATGCCCTGA GACCTTGGA 201420  
AAAATCCTAC CTGAATTGAA GAGCATCACT ATTTATCAG GAGGCGCTGC CATTTTCTTT 201480  
TTCACCTCGG TTTTATCTTG AGTGTA AAC AGCTTCGCA ATCACTTTTT CTGTTTCTG 201540  
TAATGAGCAT ATGGTGGCCT CATTCTGTG ATAATCTGA GCCACCACGA TATTTGACTT 201600  
TTCACAATTT AATTTATCTG AACCTCTAT TCTCTGGCTA AAAAATATCC CTTACTTGGA 201660  
CTTCTTTATT TTATTTTCAA TTCCCTTACC AGCACTAGCA GGGGACTCTG TACTCATCTG 201720  
CTGGCGCTGC CATAACAAAG CACTGCAGCC TGGGGGGCTC AAACCACAGA ATTTATTCTC 201780  
TCACAGTCCT AGAGGCTAGA AGTCCAAGAT CAAAGTGTGG GCAGGGTCGG TTTCTCCTGC 201840  
AGCCTCTCTC CTGGCTTAT AGAGTGCCAC CTTCTACCTG TGTCTTCACA TCATCACCTC 201900  
ACTGAGCATG TCTGTGTCCA AATCTCCCT TCTTATAAGA CCCCAGTCAT ACTGGATGAG 201960  
GATCCACCCA TATGAGTTCA TTTTACCTTA ATTATCTCTT TAAACACCCT GTCTCCAAAT 202020  
ACAGTCCCAT TCTGAGGAAC TGAGAGTAAA GATTCAACAT ATGAATTTTG GAAGGGACCT 202080  
AATTCAGCCC ACAACACCCT CTTTGGGAT GTTATTTTC CCCCTTAAGG AGCTAGTTAG 202140  
GATGTCTTAT CTCATGAACA TGA CTGTGAA CAGGAAAACA GGGAGAGAAT GAAGCTGGCC 202200  
AAGGAACAGG GCTGGTGTCA GCTAGCAGTG CTTTCTGAT GTGAGTGGGT CCCACAGGGA 202260  
GCTTGTTAAA ATGCAGATTG TGATTCATTA GGTTCAGAG GGACCTGAGA TTTCCCATTT 202320  
CTGACAAGTT TCCAGTGTGG GGGCTGATGC TGCTGGTCCA CGGACCATAC TTTGAGTAGC 202380  
AAGGAGCTTG ATACATAATG GCTGAGTGAC TTTCAGACTC CTGCTGTAGA AAAATTATGA 202440  
GTTGGCTGGG CGTGGTGGCT CACGCCTGTA ATCCCAGCAC TTTGGGAGGC CGAGGTGGGC 202500  
AGATCACCTG AGGTCAGGAG TTCGAGACCA GCCTGGCCAA CATGGTGAAA CACCATCTCT 202560  
ACCAAAAATA CAAAAATTAG CCAGGTGTGG TGGCAGGTGC CTGTAATCCC AGCTACTCAG 202620  
GAGGCTGAGG CAGGAGAATC GCTTGAACCC GGGAGGCAGA GGTTCAGTG ATCTGAGATC 202680  
GTGCCACTGC ACTCCAGCTG GGCAATAGAG CTTGACTCAG TCTCAAAAAA AAAAAAGAA 202740  
AAGAAAAAGA AAAATTATGA GTTATATTAT CAGCATATGG GGTGCCTTTC AAATTGATAA 202800  
AATTTCTAAT ATTAACCTG TGGATGCCAA ATGCTGCTCT CTGATTATGG CAGGAAACGG 202860  
CACTTGGCAG TACGAAGTTA GCTGTTGGGC TGAGCTGGCT CATCTTGTTG TGCGGTCTCT 202920  
ATTGCCTAAA GATGCCCTCC CAGGATCTTT ACTACAATC CTCCTGAGTC ATTTGGACTT 202980  
TCCCAACCTG TTATCACCTC TCAGATGGGC CAGCCATGGA GGCAGTCAGA GGAGGGCTCT 203040  
GCAGAGGGAG GGCAGAAACA GGGTGGCCTC TGCATGCCAT TAGGAGGTCA CATCTCACTG 203100

FIG. 6.77



GGGGATGCAG TTTAGGATTT AGTGCCTTGG AGAGAAGGAT AGAGTATATT AAAACATGTC 203160  
TCCGCTAGGC ATGGTGGTTT ACGCCTATAA TCCAGCACT TTGGGAGGCC GAGGTGAGTG 203220  
GATTGCCTGA GCTCAGGAGT TCAAGACCAG CCTGGCTAAC ATGACGAAAC CTCATCTCTA 203280  
CTAAATACA AAAAGTTAGC TGGGAGTGGT GCGTGCGCC TGTAGTTGCA GCTACTTGGG 203340  
AGGCTGAGGC ATGAGAATCA CTTAAGCCCA GAAGACTGAG GTTGCAGTGA GCCGAGATTG 203400  
CACCCTGCA CTCCAGCTTG GGCTACAGAG TGAGACTCTA TCTCAAAAAC AAAGAAACAA 203460  
ACAACAACAA TAACAACAAA AACCAAGTCT CTCCCTCCAC TCAAAAATGC AAGGGCCTGT 203520  
CTCCATTGC TGGGTGCCCA GGTCTCATGA ATGTAGATAT GAATTATTCC AGTCAGCCTC 203580  
AGGAGAATAG AATGAGCCCT CAGATGCCGA AGCACCTTTC AGATTCCACC GGTTTTATCG 203640  
GCTCATTTAA ACTTCACTTC TAACACAGTC CTGCATTACA CACGTGTCTG TCGTTATGGG 203700  
CAGCTGCAGA GAGGGTCTTA ATGGTCCTAA TGCTCAGTGA GGATGCCCAA TGGTCAACAG 203760  
AACCTGCCAT CTTCAGGCCA TCAAGGAGCT CTGGAGTTAA GGAAATCATG AGAGCACAGA 203820  
GGGGCGGGTA CAGCAGAGCC CTCGTGGTAA TGGGTTTTGA GGTCTAGGCT CTCTTCACTT 203880  
GGGTTTAAA TAAGTTCAAT GACTAGTAAT AGCTGAGACA CTTCTACCCT TCAATGAAG 203940  
TAAATGGGAA AATGGAGCAT TGTTGAGTCC AGGGAGCTAT AATTTAAACC CCATATATCT 204000  
AAAAGGGGTA ACATTTTTGT GTGTGTGAAA TTGGTGTCAT TCGCACTGCA TCTACAGTTT 204060  
TCTTTTCTCT TCTCTCCAG CACCCCTGGC TACATATTTG GGAAACGCAT CATACTCTTC 204120  
CTGTTCTCTA TGTCCGTTGC TGGCATATTC AACTATTACC TCATCTTCTT TTTCGGAAGT 204180  
GACTTTGAAA ACTACATAAA GACGATCTCC ACCACCATCT CCCCTCTACT TCTCATTCCC 204240  
TAACTCTCTG CTGAATATGG GGTTGGTGTT CTCATCTAAT CAATACCTAC AAGTCATCAT 204300  
AATTCAGCTC TTGAGAGCAT TCTGCTCTTC TTTAGATGGC TGTAATCTA TTGGCCATCT 204360  
GGGCTTCACA GCTTGAGTTA ACCTTGCTTT TCCGGGAACA AAATGATGTC ATGTCAGCTC 204420  
CGCCCCCTGA ACATGACCGT GGCCCCAAAT TTGCTATTCC CATGCATTTT GTTTGTTTCT 204480  
TCACTTATCC TGTCTCTGA AGATGTTTTG TGACCAGTT TGTGTTTTCT TAAATAAAAA 204540  
TGCAGAGACA TGTTTTAAGC TGATAGTTGA GGGGTTTTGT TAATGGCTTT TGGGGGATTT 204600  
ATCTCTATAC CCACAAACGA CTAGTTTGTT TTCCTCAAAC TAAATGATAA TATTAATAAT 204660  
ACACATCCTG GCCAGGTGTG GTGGCTCATA CCTGTAATCC CAGCACTTTG GGAGGCCGAG 204720  
GCAGGTGGAT CACTTGAGGT CAGGAATTAA GACCAGCCTG GCCAATATGG TGAAAGCCTG 204780  
TCTGTACTAA AAATACAAAA ATTAGCCAGG TATGCTGGTG GATGCTTATA ATCCCAGCTA 204840  
CTTGGGAGGT TGAGGCAGGA GAATTGCTTG AACCCGGGAG GTAGAGGTTG CAGTGAGCCA 204900  
AGATCATGCC ACTGCACTCC AGCTTGGGCA ACAGAGTGAG ACTCCATCTC AAATTAATAA 204960  
AAATACACAT CTGGCTTCTG GAAAAATTAC TTGAAGATCT TTTATGACAT CCATCCCTCT 205020  
TCACACAGCC ATGTGAATTA GGTTGGTATC TTCATATACT AGCATCGTGC CCAGCACTTC 205080  
CATGTTATAC AGTTTAAAT GTTCTGTAAT TCCCTGTGGG AACCTAAGAT AATGCGAGGA 205140  
CCGTCATACG TGCCCCCAA TATTGGCAA CCAATGAATA AATGAATGAA TGAGTTTATG 205200  
AATCGCTAAC TGGCTGTATT TAATGAAGTA TGTGTGTTGA GCCATTTCCC ACAGTGTGGA 205260  
CAGATTTGTC CCACAATATG GGCCTCTTCC CAAAGGCCCT ACCACCTAAT GCCATCACAC 205320  
TGGGGATTTG ATTTCAACAT GTGAATTTGG GGAGAGTGCA AACACTCAGA CCATAGCACC 205380  
ATCTCAGTAA ATGTCCCACT GGTCACCTCAG TTCATAGTGA CAGTGATCCA GCCACTGTCA 205440  
TGACAGGTGC CACTTGGCAG AAACAGCACA GCTTGGAAGA TGGCGGGGTG TAGTCAAGAT 205500  
TCCAGGATCC CCAACAGAGA AGCCAGCTCT TATAGGGGAG CCATTTCATCA GGATTGAAC 205560  
CTCAATCGAG CTGGACAGTA ATAGGTGGGT CTGTGTTATT CCCAGATGA GTATCATGAC 205620  
AGTCACAATC CTAGGAAGGA TGTGAAGCCT CCCCAGCTC TCCTCCAGTT GCCTGCTTGG 205680  
GCAGCAGAGA TGATGGAATG TGGAGTCTGG CGTGGTCTGA GGCCTGAATC CATGTGCCTC 205740

FIG. 6.78

ATGTATGATG CTCAGGCAAG AGGATCTCTC AATTC AAGGG AGAGGGCCTG AATGAGCCTT 205800  
GCTTTCCAGG CCTGTCTGAT GGTCCAGGCT GAAGCCCCCTC CTGGCTTGCA CTGCCAGACC 205860  
TCATCCAGCA GGAGCTCCTT GGCATTGACT GCTTCAGGAT AGTTGCTTCT GCTCTGAGTG 205920  
CTCTCTAAAG AGCAGTGCTC TACCATCCAA GCTGGGCTTT TCTTTTCTTC TTGCTGATAG 205980  
GGAAGGCATG GGACATTGCA GGATGGAAGT GGCCCCCAGG CCTTCTCATG CCTGGGCTTG 206040  
GTTTGAAGG TGGTCAGGTG ATCAATAATC CTGATTGGCC TGGCATTGAG GAGTTTTCCT 206100  
GGGATGTGGT CCTTTCGGTT TTTTAAAAAT TATTTTATT GATACACATA TTTGTAGGTA 206160  
TTTGTGGGGT GCATGTGATA CTTTATTATG TGTGTGGATT GTGTAATGAT GAAGTCAGGG 206220  
CATTTAGGGT CTTTCATCACC TTGATTATCA TTTCTATGTG TTGAGAACAT TTCAAGTTCT 206280  
CAGTTCCAGC TATTTTGAAA TAGACAGTCC ATTTTGTTAG CTACAGTCAC CCAACCCGGC 206340  
TGTCAGACAT TGGAACCTAC TCCTATTGAA CTGTGTATTT GTACCCATTG ACCAACTCT 206400  
CTTTGGGCTT TCAGTTTTAC AACTGGGATG ATCCTGGGAA AACTAAAGTA AATCAGACAC 206460  
CCGACGTGTG AGCTAGGTTA TAATATGCCC AGTGGACCCT GGGGACATCT TAGCTTTCAG 206520  
AGGTCATGCT GTCCAAGCTG ACTGTGGGGC TTCCAGAAGG TGGGGAGAGG AAATGATGCA 206580  
ATGGCCCATC AGAGGCACTA CTTGGGGCCT GGGGCCAGAG TGCATGTCTA AGGCATTAAG 206640  
GGGAGGGGAG AGCAGCCTTC ATAATTATGA AGAGGAGTCT CAGGTGCACA GCTTCTGATG 206700  
AGGGACAGCT TCTAATTGAA GACAGCATTG TGTAATGCTC AAACCTCCCTG TCTTCAGAGT 206760  
GCCTGCTGTA TCCCACCATC AGTTCTGTGA CTTCTCCCTA AGCCTCAATT TTGCATGTGT 206820  
TACATTGGGA TAATAATAGT GCCAACTCA TGGGGTTGTG AGGAATAATG AGGTAAAGCA 206880  
ATTGAAAAGG TTAGCACAA TATAAGTGCT CAATAAAAGC CATTATTATT ATTTTATTAC 206940  
ACTAGTTTTT AATTCCTGCA TAGCAAATTC TTGCAAATGT AGGGACTCAA AACAAATATA 207000  
ATTTATTATC TGACAGTTTT TCTGGGTCAG AGGTCTTACT AGGCTGTAAT CAGAGGGCAA 207060  
CCAAAGCTGT GATCTCAGCT GAAGCTCAGG ATTCTCTTCC AAGCTCACTG GTTGTGCGCA 207120  
GAATTCAGTT CTTTCCAGTT GGAAGACTAA AGCCTACAGT CTTCACTCTC TAGAAGCCTT 207180  
TTCTCTGGCA CAGGTTTCTC TACAACATGG CCATTTATGT CTTTAAGGCC AATAGGAGAA 207240  
CATGATTAGC ATATTTTTTT TAAGTGAAGT TTAGACCTT TTTTAAAGGC CTATCTGATT 207300  
AGGCCAGGCC CAAGTGAGCT TTAAGTCAAC TGATTAGAGA TCTTAATTAC ATCTGCAAAG 207360  
TCCCTTCATG TTTACCGTAT AACATAACTT AGTGAAAGGA GTGAAATTGC AACCAGGTTT 207420  
TGCCTGCACT CCACGGAAGG GGATTCTGCA GAAGTGTGGG TCACGGGGGGG GTTATTTTGG 207480  
GATTCTGCCT ACGTCACTGA GTCAAAAGAA GCTGAATGGT TGTGATGCTG AGGTTTTTGG 207540  
GCAGCAGCAG TGTGTGTGTG TGAGTGAATT CACACGTATG ACCACCTGGG AAGAAAGGAG 207600  
GCTGTGGTTT CCTCCACCTC CTGGCAGACA GAGAAATTTT TTTTTTTTTT TGAGACAGGG 207660  
TCTGGCTCTG TTACCCAGGC TGGAGTGCAG TGGCTTGATC TCTGCTCACT GGCTCACTGC 207720  
AGCCTCTGCC TCCCAGGTTT AAGTAATTCT TGTGCCTCAA CTCCAAGTAG CTGGGATTAC 207780  
AGACACACAC TGCCACGCTT GGCTAATTTT TGATTTTTTA GTAGAGACGA GGTTTTGCCA 207840  
TGTTGGCCAG GCTGGTCTTG AACTCCTGAC CTCAAGTGAT CCGCCACCT CAGCCTCCCA 207900  
AAGTGCTGGG ATTACAGACG TGAGCCACCA TTAACCATTT TTCTATCTCC TGTGGGAAAG 207960  
GGCACAGTGA AAGAACAGAT GAAGCTGAGA CATACAAGTG AACTCCTCCC TCCTCTCCAT 208020  
TTAGACTAAA ATAGGATTAT TCATACTGAG ATTCTCCCTG GTTGCAAAGA GATAATCTGT 208080  
GCAACTGGGT TTTTACAATT ATCCCTACCC TATGCTTTCC TCATCTGTCT TCCTCGTAGT 208140  
CAGCTCAGGC TGCTATAACA AAACACCATA ACTGGGGGCT TTTGAACAAC AAACTTTTAC 208200  
TTCTCACAGT TCTAGAGGCT GGAAATCCAA GATCAAGTTT CTGGCAGATT CGGTGTCTAA 208260  
TGAGGTCCTG CTTTCCAGTT TATAGACAGT GCCTTATCGC TACCGCCTTA CACAGTGGAA 208320  
GGAGAGGACG AGAAGCTCCT TGGGCTTTTT TTTGTTTCTT TCTTCTCTC TCTCTCTCTT 208380

FIG. 6.79

TTTTTTTTTT TTAATAAGGT CACTATCTTA GTCCATTTTG TGTTGCTAAA AGGAACATCT 208440  
GAGGTTGAGT AATTTATTTT ATTTTAAAAA GTGGCCAGGC ATGGAGGCTT ATCCTGTAAC 208500  
CCTAATCCTT TAGGAGGCCA AAACAGCAGG ATTGTTTGAG GCCAGGAGTT CAAGACCAGC 208560  
CTAGGCAAGA TAGTGAGACC CCATCTACCC CATCTCTACT AAAATTTTAA AAAATTAGCT 208620  
GTGTGTTGTA AAGTGTGCTT GTAGTCCCGG CCACTTGAGA GGCTGAGGTG GGTGGAGTTC 208680  
AAGGCTGCAG TGAGTTATGA TTGAGCCACT GCACTCCAAC CCGGGTAACG GGGCAAGACC 208740  
TTGTCTCTAT TTAATAAAAA AAAATCTTTA TGTGGCTCAC TATTCTGGGT GGCTGGAAAG 208800  
TTCAAGATTG GGCATCTGCA TCTGGTGACA GCCTCATGTC GCTTCCAGTC ATGGGGGAAG 208860  
ACGAAGGAGA GCTGGCACGT GCAGATATCA CGTGTTGAGG GCAGAAGCGA GAGAGAGAGG 208920  
GGAGAGATGC CAGGCTCTTT TTAACAACCA GCACTGGGGA AACTAATAGA GTGAGAGCTC 208980  
ACTGACTCCT GAGGGAGGAC ATTAATCTAT TGATGAGCGA CCTGCCTCCA TGACCCAAAC 209040  
ACCTCCAACG ATACCCACAC TCCAACACTG CCACACTAGG GATTAACCTT CAACTTGAGA 209100  
TTTAGAGGGG GGAAACTTAC AAACATCGC AGGCACTAAT ACCACTCATG AGGGCTCCAC 209160  
CTTCATGACC TAATCACTTC CTAAAGGCCT TACCTCTTAA TCTCATCACA TTGAGGATTC 209220  
GATTTCAACT TGAATTTTGG GGGGACACCA ACATTCAGGC CATAGCATCA TCTCAATAAC 209280  
TGTCCTATTG GTGGTCACTC AGGCCCAAAA CAAAGGAACC TTCCTCCATT CTTTCCGCC 209340  
CTCCACCCCA CAGTCAATCA TCCCCAAGCT CCATCAGCTC CACCTTTAAC GGCCAACCCA 209400  
CCTCTGCCAC ATCTACCAT CTCCACTGCT ATCCCTGTCA CCTGGGCCCA CCATTCTCTC 209460  
TCCTGGACAG TCTCCATAGC CACCTCTGTC AGATTTATTT TATTTTTTTA TTTTTTTTTT 209520  
TGAGACAGGT TCCTGCTCTG TTGCCAGAC TGGAGTGCCA TGGCATGATC ACATCTCACT 209580  
GCGGCCTCCA TCACCTGGGC TCAAGCAATC CTCCCATCTC AGCCTCCCAA GTAGCTGGGA 209640  
CTACTGGCAC CACCATACCT GGCTAATTTT TTGTTGTTGT TGTTTAATTT TTAATACAGA 209700  
TGAAGCCTCA CTATGTTGCC CAGGCTGCTC TTGAACCTCT GGGCTCAAGT GATCCTCCGG 209760  
CCTTGGCCTC CCAAAGTGCT GGGATTACAG GCATGAGCCA CCGTGCCAG CCCATCAGAT 209820  
GTTAATGCTA CACGCACTTG CTTAAATCC CCCAGATAAT TCTCGCTGCT CTTGGAATAA 209880  
TTCCACACA CCTTGGCGTG GCCATGCAGG CTCTGTGCCA TCGGATATGT CCCTGCCCCC 209940  
TCTCCCAACT CCTCCTTCG CTTGCTCGTT CACTCAGTTC CAGCCACATT GCCCTGGGAG 210000  
CTGCTCCAC CATGGGGCTT CCTAATGCAC TGGTCTCTCT CATGCAGTGG GGCCTCTCCC 210060  
TCCTTTTACT CAGTGTCTCC CAGCACCCAC CTCCTCCAGA GCCTTCCCTG ACCACCACAC 210120  
CTACACCTAG GCCCTTCCTC CTCCACGCTC CCTCCTCCAC CCCGGCCTCC TACCCACGTG 210180  
TCACTTCTTT ATACTCGCTG CCACCTGAAA TTAGATCATT TATTTACCCC TTTATTTGTT 210240  
CAGTTTGCCT TGTCGGTTAG AATATAAGCT TCAAAGGGC AGGAGCTTTG CCTATATTGT 210300  
TAGGCCGGGC ATACAATGAG CACTCAAAAA AATATTTGAT GAGTGTATGA AAGAACAGAC 210360  
TGGGTTATGT AATTGTGCCT ACTTACCTAT ATGACCGTGT GGTGGGGTTT ATGGTGGGTG 210420  
TGGTGGTGAT GGCTATAGGG CTATAAGCAA ATTTGGGACA GGGAGTCTAA GAAATGTTCT 210480  
TAAATTTTAG TAAGCAAAGC ATCCTCTACA GAACCTGTCT TAAACATGA AAGTTCCTTA 210540  
GTGCTACCCC CAGAGGTATG ATTTGGTAGG TCAAGGATAG GGCCTGGAAA TTCACATTCT 210600  
TGTTAAGATG TTCTTCATCC GGGGTTTGTG GACCACCTTT TCAGAAGATT TTTGCTCTGT 210660  
AGCTGTACTA CCAATGCAG TAGTTCGTAG TCAGTGTGGC TCCTGAGCCC TTGAAGTGTA 210720  
GCTCCTCTGA ACTGAGACGT GCTGTAAATG TAAATTGCAC ACCGGAGTTT GAAGAGTTAA 210780  
TACAAAGAAA AAGGAATGCA AAACATCTCA TTAATAATGC TTTACACTGA TTACATATTG 210840  
AAATGGTAAT CTTGTAGATA TAGTGCGTTA AATAAAATAT ACTGTTAGGC TTAATTCAC 210900  
GTCTTTATAC TTTAATGTG GCTACTAGAA AAATTTAAAT AACATATTCA GCTCACATTA 210960  
TACTCCTATT GAACAGAGCT GATCTATAAG TTCCATGGAA GATGGCAAGT CTTGCGAGCT 211020

FIG. 6.80

GAAATAAAGG CTGGATCCCA TTCTACGGGC TCATCTTTAG CAATGATTTT TTGCAGACGA 211080  
TATTGAAAAA TGTGGCAATG AAAGTTACCA CAAGCATCAA ACCAGTCCTG CCTAAATCTG 211140  
GAAAATAGTT ATCTGAGGCT GTTAGCATAT GATCATGAGA GCGTTTCACC ATGGATTTCT 211200  
GATCACAGAT GTGGCACATT ATTTAAATAT CACTTTTACA GTCACCCTAG AGGCTAGGGT 211260  
TATCTGAATA TGGAGAAAAGA AACAGCTTGT GGAGCTGTTG TATAAATGAA ATTACTAGAA 211320  
AGTAATGCAC TCAATTGCAT ATTGGCTCGG GGGGTTATTC TTATTAAAT GTTTAGAGAG 211380  
GACTTTCTGT TCATTTCTGC AGAATTGCTC TTCAAATTA GAATTTGCTT GACACGCTAA 211440  
TAGACCACAG TCCCAAGAGA AGTTTATCCT TTTTCTTCT TATCCTTGCT AAGCACTTAG 211500  
ATGCTCTGCT GATAGGTAGC ATATATTGTC TATATGAAGC TTTTGTGTTA ACATTGACTA 211560  
GTCCTGCAAG TTGGCACACT CTTACTTGGC CTAAGAGAAA TCAGCACCAG GCTTTAAGAA 211620  
AATCAGATGA TCTACCTAAA GGAACACAAC TCTGTCTCTC TTTTGACAAT TGTTGTAAAC 211680  
AAATTTTAAT GGAAATTTGC CTTAATTGTG AAGAAGTTGC TGCTAAAATG GACTTGCCAT 211740  
TAATGGACTG GAACCCATTG CATAAGCAGA ATGAAATATA AGCCTTCTCA GGATTACAC 211800  
TTATAAAAAA CCATTCAGCC AATCAACAAG AGGGCAAAAG AACAAACATT TGATGTGTAA 211860  
TACTTAATT TAGTGCATAT GCATTTGGGT CCTCAATGTC AGCACTATGG CAACCAGAAC 211920  
ATGGCCACAA TAACTGTCTG GAAATGTCTA TTCTTACCTG GACCCAGCAG GCCATGCCCC 211980  
ACTGATTATA TAATCTCCCT CTCTCCTTGT TACGGTCTGA ATGCTTGCAT CCCTCAAAAA 212040  
TTCATGTGTT GAAATCCTAA CCCCCAAGGT GATGATATTA GGAGGTCGGC CTTTGTAGAG 212100  
GTAATTAGGT CATGAAGACA GCATCCTCAT GAATGGGATT AGTGTCTTA TAAATAGGC 212160  
CCAAGGGAGC TCATTCACCT TGTCCACCAT GTGAGAACAC AGCGAGAGGG CACCATTAT 212220  
GCACCAGGAA ATGGGCCTTT TCCAGACAAT CTGTCGGTGC CTGGATCTTG GACTTCACAG 212280  
CCTCTAGAAC TGTGAGAAAT TAATTTGTTT TTTATAAGCC ACCAAATCTA TGGTTTTTTT 212340  
TATAGAAACC GTAATGGACT AAAACACTCC CTAATTATAT TTAACTTAT CAGTGCCTG 212400  
GGCAGTGACA TATTAAAAGA ATGCTGGCCA ACGTAATTGA CACCATAAGG CTGGATGATT 212460  
CTTGTAATTT TCAGCCTCAG AAAAAGGCTG GGGAGAGGAG TCAGGGGAAA GGAGGTGGTG 212520  
TGTGTGTGTG TGTGTGTGTG TGTGTGTGTG TGTGTGGTAC GGTGGATGCC TGCTGAGAGA 212580  
GAAAGAGCTA TAATAACATT CTGTGGTTCA GCTGACACAT CCTTCTGCA TCCCCTCAA 212640  
TCACCTGGGT TAATGGGGAC CTCGCTAATG TCTGAACCTC ATCTCATTTT AACCTTTTGT 212700  
TTCAAAGCCT CTCTTTTCAT GACTTCCCCG CCTTCATTTT TCCCATATGG TGGGGTTATT 212760  
ATTAAGACAT TAAATGAGAG TGGACAGGTA GGCAAAGGAG GTGGGTTGCA GGGGAGTTGA 212820  
GGGTTGCCTG TGTACTTTTC TAGACTGTTT CACTTCACAT CAGTGAAATA TTCCAATTG 212880  
ATACTATCAT GAAACAAAGC AAATGAAATG CTGAGCACGG AGCTTCGTCT TGATGAAATG 212940  
CTGAAAGAAA AGAAAGGAAA AATAAAGTAG CCATTATTTT TGCCCTTCCT CCCACCCCA 213000  
TGTTTACTAC TCTTATTCT CTTTGTATT GTTGTGTTGG AAGCACAGCA TCAGAAAAAC 213060  
TCCCAGTTTT GAGAGATAAC TCAGTGTTTA GTTCACTTAA ACCTGAGAAA GGAGAAGAGG 213120  
ATGCCACCGT GAGGTCCAGG ACGTAAAGAG GAAAAAACA GACAAAAAA TCCATATGAA 213180  
ATGAAAATGT GAAAGAGGCG CTTTCGAGCA GATGAGTGTT GTAGATTACA GTGTTGAGAG 213240  
CTGTTTGTGT CCAGAGCTGC TTGCTGCACC TGGCGGGATA AACACTGGTC TAACAGAGGA 213300  
TCCTTGTTTC AAGGAGGCTG CCTTTTATTT GGGGGGACAA AATTGTTCTT GAAAGCTGCT 213360  
CAGTGGTTCA AGCTACAGCA TGGTGGACTA GCAGAATGGA CTCCAGGGCC TCCGAGGAGA 213420  
CAGTGACTGC TGCCAGAAAT AGTCAAGGAT AGAAAGGAAG GACTTCACTG AGGCCTGGGA 213480  
GAAGATTATG GAATGGGACT GACAGCAGTG ACGGGGAGTA AAAGGGGGTG TCTGGGGGAA 213540  
TTGTGCCCCA TGGTGAGAGC TAGAGGGTTC ACAAAGACTT AACCCGACGC ATCTCTCTCA 213600  
CCCTGGAGAT TGGGCCCCGT CAATCTAACT GGATGGCTAT AATTAAAAG GTTTAGGTAT 213660

FIG. 6.81

TATGACAAAC ATGGATATAT TAGGTGATAG CAATGCAAAA TGCATATGGC TTCTTGATAT 213720  
AAAACACAAG ACTTGAAAGC AGCATCTTTG GCTGGGTACT ACAGCCACCC TCCTCTGTCA 213780  
CTAAGGGAGG CTTTGGTGGA AAGGGCTGAG AGCCTCTAGA CTGTGAACAA AAGTAGGCAC 213840  
AGAAGAACAG TTGGAGATAA TAAGTAAACC ATCTTGACAG GAATGAAGAA TTCCTGAAA 213900  
GGAAGGTCCC TGAGTTAGGT TGTTGGATGC TTTCAGTAGT GAGTTATTGA AAGTGTTTGG 213960  
GGGGTGTGTG TGTGTGTGTG TATGTGCAGT ATGTGTGTGT 214000

//

FIG. 6.82

Figure 7

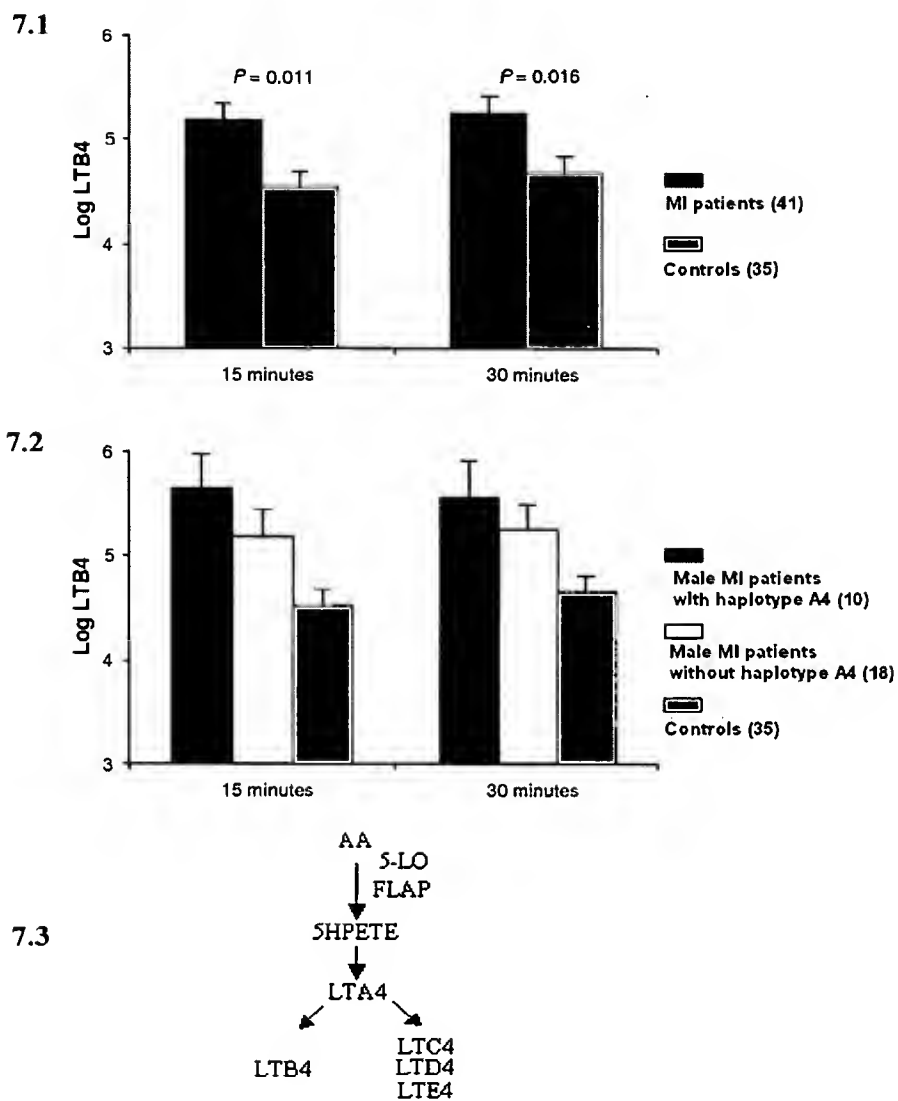


FIG. 7

SNP name      SNP amplimers

SG13S421

GATTATATCCCACCTACCACTGCAGCTCCAGGATCCAGCTTCACAA  
ACATTTGTTGAATGAATGAATAAGAAAAGAGGACACCCCCAAAGAGGCT  
GCAAGGGAAAAAGCTACAAAGACAGAAGCACCAGGAAAAAGTAGGGTC  
ATGTAAGTCAAAGCAGGAAAAAAGTTCCATGGTGGGGTGGTCAGCAGTGT  
CTAAT[A/G]CCACGAAGGCACAAAGTAGGATAAAGGTTAAAAATCAGCCT  
TTGGTTTTGGCAAATATGAAGCTTATCGGTAGCCTTAGCGAGAACAATTCC  
ATCAGGGAGCAGAAGCTAACTGCAGTGGGTTGAGTCATCAAGCAGGCAT  
AAGGAAGTAGGGATACCCCATATAAGCTACTCTTTCAAGAAGCTCAAAT  
CTGAAG

SG13S417

ACAAAAATTACCATCATATGCTGTCATGCATGTCTGCCAGTCTATTT  
ATCATATTATTTAAGAAACAAACATTTATTGAAGATTTATCATGTGCTCAG  
CACTGCCAAAGAGGAAATAAAGAGCATAATATCTATTCTTAGAAAAATAAC  
ATTAACACAAATAGAAAACAAGAAACCATAATGTAAAAAATATTACATAG  
[C/T]AACACAGAAAGACAATGTATAATTATACATACGCACTAAAGCAAAG  
ATAACATAATTTATAAATTATGAGGTACAGAATAGTTAGATTCTGAAAAT  
TAAATAATCAGGAAAAACTTCATGAAGATGAGATCTGGGCTGGATCCCA  
AAGGATAGGCAGGTGGATCATGTAGAACAGGGGAAAGGAGTTCCTGATC  
GG

SG13S418

AACTAAAGAAAGCCACAAAAGTTCACCTCAATGCCAAGACATTTCT  
TGATTTTTGAAAACCCAGTTGTGCGAACCACCCATCTATAGAACTTGAAA  
GACTAAAACTATCTTACTCTAAACATTTTCTAGGAAGTTGATTCTACAAC  
ACATTTTGGTTTTTCCAATTTGGCTTCTAATAATTATTTCAAAGTTTCTGTG[  
A/G]CCTAAATTTTGTTTTACATTGATCCTTTGAATGGACTACTGTTTCCACA  
TTTTAGAACATTTAAAAAGATATCTACAACCCGAGTCTAATCATAAAAAA  
AATCAGACAGATCCAAAATGTGGAACATTCCACTAAAAAAGGAGTGGGG  
AGAGGTCTTTATTCTTCCAAAAATATCAATGCCATAAAAGACAAAGACG

SG13S44

ACCCTTCAACCCCAGCCCAGCTGCTAACTGACTACAGCCACATGAA  
CAGAACCAGGTGAGACCAGAGGAAACTTCCAGTCACCTACCAGATCATGA  
CAAATAATAAACGATGTTTTTTAAACCACAAAGATTTGGAGCAGCATTG  
TTACACAAAATTAGACAACCTATTACAGTTCGACTAAAAACATGTTTCATTTA  
C[A/G]ATACTAAATTAGAAGTGTAAGAATGGGAGAAAAACTTCATACTTTA  
AAAGTCATTTTTTCCTCCAAAAACTTCCAACCTTGAAAAACTGATTTTTAT  
AATGCATAAAAAATTAAAATAACCTTAGAATTTATATGAGTAGCATAGCCA  
GCTGGCTTTATTATCTGTTGTACTCAACACTTCAATAATCACTGATGTTT

SG13S45

ATGACCTTACCTCGTTTTGTTTTCTTGTCTGAGAGAAACACATTAG  
CAGTCTCCCATCTTGTTTTTCTTTCTGTCACCCAGGACAGAGGGCAGT  
GGTGTGATCACAGCTCTGCAGCACGACTTCCCCAGGTTCAGGTGATCCTCC  
CACCTCAGCCTCCCAAGGAGCTGGGACCACAGGCACATGCCACCACGTC[  
C/G]AGCTTAATTTTGTATTTTTTTGGTAGAGATCAGGTTTTGCCTTATTGCC  
CCAAGCTGATCTTGAATTCCTGGGCTGAAGCAATCTGCCTGCCCTGGCCTC  
TCCAAGTGTTAGGATTACAGGTATAAGCCACCGTGCAGCCTTATATTTTGT  
TTTAAATTTTCTCTGTATTTTTTCTCTCTGGCAAATTGTTTAGGGA

FIG. 8.1

SG13S46

TTTTTTGGTAGAGATCAGGTTTTGCCTTATTGCCCCAAGCTGATCTT  
GAATTCCTGGGCTGAAGCAATCTGCCTGCCCTGGCCTCTCCAAGTGTTAGG  
ATTACAGGTATAAGCCACCGTGCAGCCTTATATTTTGTTTTAAATTTTCCTC  
TGATTTTTTCTCTCTGGCAAATTGTTTAGGGAGTTTCTTTAGTTTATC[A/G]  
GACTAAATTTCAAGGCTTTCCTTCCAATTTTGACATGTAAACAGTCCCTCA  
TTTCTGCTTATCTAGTGATTATCCCAAATCTGTGTTTACAGTCTAGCTGTC  
TCTCCTGAGATTAAGACTTGTTTCTCTAACTACCTGACGGCAGAATCTCCT  
CTTGGAAGTATCAAGGAGGCAGTTCAAAACTGAACTGGGCATT

SG13S50

GCTGATCTTGAATTCCTGGGCTGAAGCAATCTGCCTGCCCTGGCCT  
CTCCAAGTGTTAGGATTACAGGTATAAGCCACCGTGCAGCCTTATATTTTG  
TTTTAAATTTTCCTCTGTATTTTCTCTCTGGCAAATTGTTTAGGGAGTTTC  
TTTAGTTTATCAGACTAAATTTCAAGGCTTTCCTTCCAATTTTGACATG[C/T]  
JAAACAGTCCCTCATTTCTGCTTATCTAGTGATTATCCCAAATCTGTGTTT  
ACAGTCTAGCTGTCTCTCCTGAGATTAAGACTTGTTTCTCTAACTACCTGA  
CGGCAGAATCTCCTCTTGGAAGTATCAAGGAGGCAGTTCAAAACTGAACT  
GGGCATTGGCTCCACTCCTTCTCCTTCTCTTACTATTAATACCC

SG13S52

TAAGTCTTATTTAGGCATCGTTTCTTCTGGGAGACCTTTGTAGAATC  
TCTGAGGTTATGTTAACATGCTAAGGTTTTCTTGACATTCTCAGATTGGGT  
TAGGTGAACTTTTAGCAACTTATCTTTTACTAAAAAGTCATCCCTCAGTA  
TCTGTGGGGAATTGGTTCTAGGACTCCCTAAGGATATCAAAATCTGCAT[A/  
G]AGCAGCCCAGGTGAGACCAGCAGAAGCACTTACAGTCACCTACAGGA  
TCATGACAAATAATAATCATGTTTAAGCCACAAAGTCCTTTACATAAAA  
TGGTATAGTATTTGCATATAACCTACACATCTTCCTGTATCCTTTAAATCAT  
CTCTAGTTTATAATACCTCATACGATGAAAAACTACGTAAATAGTT

SG13S53

AAGCAGTTCCTAATTACTGGACATTCTCAGATCTGCTAGAGCTACA  
TGTCCAATTACGAGAATATACTGGAAAAAGCCCTGGATTAGAAATGAGAG  
GATGTAGGTTTTAGTACCAGGTACGCCACCTTGTTAATGCAAATTTGAGTA  
AATTGTTACTTCTTTTAGGCCCTGTTTTTGCTGTTTTGTTTTCTGACAGT[A/  
C]TGGTCTCTGTGGTCCAGGCTGGAGTGCAGAGGCACAATATCAGGTCCCT  
GCAGTCTCTACCTCCCAGGATCAAGCCATTTTCATGCCTCATCCTCCTGAG  
TAGCTGGGATTACAGGCATGTGCCACCACACCCTCGAACTCCTGACCTCA  
AGTGATCTGCTTGCCTCAGCCTCCCAAAGTGCTGGGATTAGAGGTGT

SG13S55

GAATATACTGGAAAAAGCCCTGGATTAGAAATGAGAGGATGTAGG  
TTTTAGTACCAGGTCAGCCACCTTGTTAATGCAAATTTGAGTAAATTGTTA  
CTTCTTTTAGGCCCTGTTTTTGCTGTTTTGTTTTCTGACAGTATGGTCTCTG  
TGGTCCAGGCTGGAGTGCAGAGGCACAATATCAGGTCCCTGCAGTCTCT[A/  
G]CCTCCCAGGATCAAGCCATTTTCATGCCTCATCCTCCTGAGTAGCTGGG  
ATTACAGGCATGTGCCACCACACCCTCGAACTCCTGACCTCAAGTGATCT  
GCTTGCCTCAGCCTCCCAAAGTGCTGGGATTAGAGGTGTGAGCCACTGTG  
CCTAGCCTTACACATTGTTTTCTTACTGGTAAAGTGGGAATATCTAGA

SG13S56

GTTTTGTTTTTCTGACAGTATGGTCTCTGTGGTCCAGGCTGGAGTGC  
AGAGGCACAATATCAGGTCCCTGCAGTCTCTACCTCCCAGGATCAAGCCA  
TTTTCATGCCTCATCCTCCTGAGTAGCTGGGATTACAGGCATGTGCCACCA  
CACCTCGAACTCCTGACCTCAAGTGATCTGCTTGCCTCAGCCTCCCAA[

FIG. 8.2



G/T]TGCTGGGATTAGAGGTGTGAGCCACTGTGCCTAGCCTTACACATTGTT  
TTCTTACTGGTAAAGTGGGAATATCTAGAAGTTGCATGCTACATAAATTCA  
ACCATATATTATTGGCAAAAAATTTTAAAGAAAAACATCAGCTTAAGAGT  
ACTAATTGAGTACATGCCTTGGAATGAGCATGAGCTGGAAAGAACAAA  
SG13S57

GGCAAAAAATTTTAAAGAAAAACATCAGCTTAAGAGTACTAATTG  
AGTACATGCCTTGGAATGAGCATGAGCTGGAAAGAACAACCTGTTGTTA  
CATCACTCATTGCTGTTTTTCATATGCTGCTCATTGTAAATCTTGCTCAGTGG  
CATGATTTTAGTGTTTAAAGATTTATTTGTTTGTTTGTAGGACAAAGTC[  
C/T]CTACACATAATCTACTTGCTTCATATATACATACTTATGCATATTATGT  
ATGTACATACATGCTCTCAGGGCTCACATGAAAAAACAGCCATTCAGGTG  
ATGTGATTTATCTCATATGCTTACTTTAGAGTCAACAGGGTGTGACTCCA  
CTATACAATACTGGCATGGAGAACACATAAGTCAAAGTAGACAGGAC  
SG13S58

TTTATTTGTTTGTTTGTTTAGGACAAAGTCTCTACACATAATCTACT  
TGCTTCATATATACATACTTATGCATATTATGTATGTACATACATGCTCTC  
AGGGCTCACATGAAAAAACAGCCATTCAGGTGATGTGATTTATCTCATAT  
GCTTACTTTAGAGTCAACAGGGTGTGACTCCACTATACAATACTGGCAT[  
A/G]GAGAACACATAAGTCAAAGTAGACAGGACCCAGCCGTACCATTGGCT  
AGGGCACAAATATATTCACATATGTGGAGAATGATGTACGTAGAAAGGTC  
TTCATTGCACAATGCTCTTTAATAAAGATCTGGAAAAAAAACACCTAA  
ATGTTCAAAGGATAGGGTAGATGAAATAATGGTACATTATAAAATGGAA  
SG13S59

TCTGTCACCCAGGCTGGAGTGCAGTGGCATGATCATGTCTCCTTGC  
AGCCTTGACTTCCCTGGCTCAGGTGGGCCTCCACCTCAGTCTCCCAAGTA  
GCTGGAACACAGTCGTGCACCAACCATAGCCAGCTAAGATAGTGAGATGG  
TGGCCCCACTGTCTTGCCCAGGCTGGACTCGATTTCTGGGTGCAAGCACC  
[C/G]TTCCCGCCTCAGCCTCCCAAAGTGCTGGGATTACAGGCATGAGTCAC  
CATTCCAGCCTACTTGTCTTTAATCTTAAAAATATTAATGTTGAGTTTTGT  
CTCCCAGCATGTGGGAAAGATGTCATCCATTGCTTCTGTTTCTGGAGGCC  
TGGGAGCAAGGAGCCCAGGAACAGTATCACGAAGCTTGAGATAATAC  
SG13S60

ATCATTGATGGGCATTTGGGTTGGTTCCAAGTCTTTGCTATTGTGAT  
TTTTTTTTTTTTTTTTTTTTTTTAAAGACAGAGCCTCACTCTGTTGCCAGGC  
TGGAGTGCATGGCATGATCTCAGCTCACTGCAACCTCCGCCTCTCAGGTT  
CAAGCAATTCTTCTGCCTCAGCCTCCCAAGTAGCTGGGACTACAGGC[A/G]  
CCCACCACCAGGCCAGCTAATTTTTGTATTTTATAGTAGAGACAGGGTTTC  
ACCATGTTGGTCAGGCTGGTCTTGAACCTCCAGACCTCATGATCTGCCTGCC  
TTGGCCTCCCAAAGTGCTGAAATTACAGGTGTGAGCCACCATACTGGCC  
TAGGCAGTCTTTTTCAAACCTCTAAGACTGTGCTTGTGTCTCAGG  
SG13S419

TGGTATGAGGTAAGGATCCATTTTTTCCCATTGTCATAGCCAGTTT  
TTGTAGCTCCACTTTATTTTCTCACTTGATCTGCCATGCCACCTCTAGCATG  
TATCAACATATCATGTATGTGTGCAGCTGTTCCCTTAACTCTCAATTTTATTC  
TCTTGGTTACTTTGTCTAACCCAGCACTCATACTTTTTAAATTATTA[C/T]G  
GCTACCTTGTAGGGCAAGAATCCTCACTTTTATTCAACTTCTTTGAAGTG  
TCTTGATGCATATTTTTTCTGATCTTACTTGGCCATATATATTTTGGGGACA  
GATGTGACATCATACCAAGCTTCTTTGCTTGACATTGTAGATATTTCTTA  
TTCATTAATGTGCTAAAAATTTTGAAGTTGGTCATACAGTC

FIG. 8.3

SG13S61

GTTTCTAACATTATAGACACTAGTTTTAGGCTCTTGGAGGCTAGCA  
GCAATTCTCAGAGGTAATGCAAGCTTCCCCATTTCTTCCCGTAGTCCTGTG  
AAAGACCAGCCACCTCCAGAAGCCTACACATGAGTCTTCTCAGCCATACT  
TTCTGCTTTTCCCTAATGCCTCTCAGCAGCGTATTAGAAAGGCCATGATCGA  
[C/T]GTACCTGTTACCTTCAGGCTTTGCATAAGGTGTATATGAAACATAAT  
GAATTCGTGTTTAGGCTCAGGTCCCATCCCCAGGTTACCTCTTTATCTTG  
GAGACACTTCTGGTCCCATAACATTTTCAGATAAGAGATATTCAACCTGTACC  
CACCACGTAAGGAGAGGAATAGGTTTTAGAAAGAGGAGTCAGGGAGGCA

SG13S62

GCATCTATTAAAAGTGATGGTTTTAGTATCCTGTCTCATTTTTTTCCT  
TTCCTTACATCATGTATTATAGGTAACACATGCGCATGTGTGTATTTCTC  
TTTTAGACAAAGGATGAGATTACTACTGTTAGCTCAGTTTTTTTTTCCCTAC  
TTAACATCTTTGCTTTTTATTTTTTAGACATATTTCTAAGACTATTAAA[C/T]A  
TTAGACTTACGTAGCCCTTCTGTCATTGTGAAATACATAGTTTACTAACAG  
CTACCATCAAGATAAAGCCTTTATTTAAATAATTAACTTCTTAGTGGA  
GCTAAGTAAGCACAGTTTATGGATTTTGGGAATTTTGCCTTGCATTTGTC  
TGATATGGTAAAATATTGAGTTTGTTTTTCTCATAATGTTTAC

SG13S63

GATAACTCAATCCCCTTAAAGGGTTGTATCAAGCCATTGATAAGGG  
CTCACTTTGATATAACCATTTTTCTGTTATTTAGACACTCTTTCACACTTCCT  
ATTTTCCTCCTGGGGATGGTTTGAATGGATGACACAATACCATATTATAAA  
AGCACTTTACAACTGTAACCTATGTTATAAATGTAATTATTACCTTAA[A/  
G]GTTTTACCCTGTTTCAGATTTGAGTGGAAGTAGTTCTTTACAATACAAA  
ACAACTTATTTTAACTTTTTTGCATTTCAAAGAATGATCAATCCACTTCA  
GGTGCAGCATGGTTTCCAACCCTGACAGCATGGAAGAATCATTTATTTAG  
CTTCTAAAAATGTGCAGGCTGTACCCTAGACCAGCCTTGGGGATTAG

SG13S64

TCCTCTCTCTCATTCTCTCTCTCTCTCTTTCTCTCTCTCCTTCTTTG  
CTCCTTCATTCTCTCTCTCTCTCTTTTTTTTTTGAGACAGCATCTCACTAT  
ATTGCCCAGGCTGTTCTCAAACCTCTGGGCTCAAGTGATCCTCCTGCCTCA  
GCTTCCTGAGTAGCTAGGACTACAGGCACATGCTATGGCAATACT[A/G]TT  
TTAAACATTGTTTTCAAGGCTCCCCAGGTGATTCCAGTGTGGGTCATGTGG  
TAGAGAACCACTGACACAGGCAAACAAAGGATACATAAAGTTGTCTATTT  
AATGGGTAGGTGCAGGTAGTAGATAAGAGTGTAGCCACATAAACCACAT  
GCTTAGTGAACGGTTTTGTTTTGTGTGTATGTGAGGGATTAGCAT

SG13S65

TTCAAGTTCCATTTAGCACGACAGCAGGGAAGGGACTGTTGGCAG  
AAAAAACTGGGGCAGTGGGATTAAAGACAGACCACACATTCCAAAAGG  
CACCGTGGGAGGGTCAGGGGGCGAGGTTAGGTCTAGGCTTCAGTGTCTG  
GGAGACTCAGTCTTACAGGGTGACAGCGATCAAGAGTGCAGCTTAGGCT  
GGGT[A/G]CAGTGGCTCATGCCTGTAGTCCCAGCACTTTGGGAGGCCGAGA  
CGGGAGGATTGCTTGAAGCCAGGAGTTTGAGACCAGTCTGACCAACATGG  
CAAAACCCCATCTCTACTAAAAATACAAAAATCAACTGGGCATGGTGGCG  
TGTGCCTGTAGTCCCAGCTACTTGAGAGGCTGAGGCAAGAGAATCACTTG  
AACC

SG13S420

TAAATGATCATTATGTTTCATATTCACACATACAATAATGTACTCAA  
GTTTATTGCTAAGGTAATTCAGAATCTCCTTATTTTGAAGTGTGCATTTGA  
TATACCTGTTTGGGAATAACTAGTTTCTTATCTTTGACAGAAAATAATTTT

FIG. 8.4

GTTGTTTTGTTTTTACTAAAAAAGCATGGTGAAAAATGGCTCCATTTCTA[A  
/T]GAGAGGTAACATAAATATCGCAATTTGCTGGGTGTCATTAAAGTAACT  
CACAAGGGAAAAAATGCAAATTGGTATCTGCTGATGGAGTAAATCTCCGC  
AGAAGTGATGACCCTGAAAGGATCAATATATTAAGCCCCCTCCCAGCTGG  
TCATTCCAGATTGCAACAATAAAGCATTAAGTGTTAAAACCTCAAGGCA  
SG13S66

CTCATCAAGCCCACCTTTATACTTCATTTCTCCAGACTTCATGTCCA  
GACTGTGGGATGAACAAGTGGTTATAAGGTTTTAGAGGCTCCTGTAGGAC  
TAGATGGAAGGCAAAAAAAGGAAATAACCTTTAAGCATGCTCTCGATTCC  
TTAAATCCCATCTGAAAGTCTTAAGGATGTCTTCTCAGTCATACTTATTTG[  
A/G]CAATATTACCTAATTTTCTCCATTAGCCCCAAGCTCAGGGGTCTTTCTT  
CTTCCATATTCACATGGGTGCAATGGTTTTCTGAAAGGAAAACAGCATT  
CTAGGGCAGTAACATTTAATTAATCACAGGTACTTATCAAACCTACAAAAC  
AGGCATTCCAGGAAGTGGGTGTTTCTGTTTGTAATAATTACACTCTCGTG  
SG13S67

TAGGACTAGATGGAAGGCAAAAAAAGGAAATAACCTTTAAGCATG  
CTCTCGATTCCCTTAAATCCCATCTGAAAGTCTTAAGGATGTCTTCTCAGTC  
ATACTTATTTGACAATATTACCTAATTTTCTCCATTAGCCCCAAGCTCAGGG  
GTCTTTCTTCTTCCATATTCACATGGGTGCAATGGTTTTCTGAAAGGAAAA[  
C/T]AGCATTACTAGGGCAGTAACATTTAATTAATCACAGGTACTTATCAA  
CTACAAAACAGGCATTCCAGGAAGTGGGTGTTTCTGTTTGTAATAATTACA  
CTCTCGTGATCATGCTCCCACTAAAATGTAAGTTTCGCTGAGGATGGAGGT  
TTGGTCTCTTTGCTCTGTGCTGTAACCCCAACACTGCAGCAGGGCCTG  
SG13S69

GCTGCATAGTCTCACTTAGGTGTGGAATCTAAAAAAGTCAAATTA  
AAAAAATGTCAAGCAGAGAATAGAATGGTAGTTGCCAGGGACTCTGGG  
AAGTAGCAGGGGTGGGGGTGGAGGGGAGGGGATGGGCAGAAGTTGGTCA  
AAAGGTACAAAGTTTCAGGTAGACAGGTGTAAGTTCTGGGGATCTATTGT  
ACAG[A/C]GTGGTGACTGTAGTTAATACTGTATTGTGTACTTAAAAATTGC  
TCACCAAAAATGTTCTCACCAAAAAAATGATGTTTGGATATGTAAACAG  
TTTGATTTAATCATTTTGACGTGTGTGTGTGTGTGTGTGTGTGTGTGTGT  
GTATACATCAAACATCACATTATATACCATATACAATTAATATATACAAT  
T  
SG13S70

GGGGTAAATGCTGACTGCCTGTTCTCTGGACAGGAATGGAGAAGA  
TGGTGCTAGCAGGGTTGCTGTTTCATATGTAGACATTCATGCAGTCACTCTC  
TTTTCAGCACACTTCTTACTTCTGCCCTGGGTTCAGTTGCTGACTCTGAGCC  
CAGAAACCTTCTAGGGTTCTGTTAGGTAGATTGGCTTCCACCGTCTTTGC[  
A/G]ACAACCACAGAAAATTCTAGACTGTTTTCTCTTCGGGCTTCATTAGTC  
AACTTGCTTCAGTCTGTCTTGCATCTTCTAAATATTTATAGATCTCTCTCTT  
TTGTTGGAGTGGCAGAAAATGCTAGTTGACCACCCAATATTCAAATTATC  
CTGCCTCCTTAATAACAGAATATCATTGGATGTGGTGGGTAAATAAT  
SG13S71

ATGGAGAAGATGGTGCTAGCAGGGTTGCTGTTTCATATGTAGACATT  
CATGCAGTCACTCTCTTTTCAGCACACTTCTTACTTCTGCCCTGGGTTCACT  
TGCTGACTCTGAGCCCAGAAACCTTCTAGGGTTCTGTTAGGTAGATTGGCT  
TCCACCGTCTTTGCGACAACCACAGAAAATTTCTAGACTGTTTTCTCTTC[A/  
G]GGCTTCATTAGTCAACTTGCTTCAGTCTGTCTTGCATCTTCTAAATATTT  
ATAGATCTCTCTCTTTTGTGGAGTGGCAGAAAATGCTAGTTGACCACCCA

FIG. 8.5

ATATTCAAATTATCCTGCCTCCTTAATAACAGAATATCATTGGATGTGGTG  
GGTAAATAATATACCCTAACTTTCCTTGCAGAGAGGGGTGGCCAA  
SG13S72

CAGGGTTGCTGTTTCATATGTAGACATTCATGCAGTCACTCTCTTTTC  
AGCACACTTCTTACTTCTGCCCTGGGTTCAGTTGCTGACTCTGAGCCCAGA  
AACCTTCTAGGGTTCTGTTAGGTAGATTGGCTTCCACCGTCTTTGCGACAA  
CCACAGAAAATTCTAGACTGTTTTCTCTTCGGGCTTCATTAGTCAACTT[G/  
T]CTTCAGTCTGTCTTGCATCTTCTAAATATTTATAGATCTCTCTCTTTTGT  
GGAGTGGCAGAAAATGCTAGTTGACCACCCAATATTCAAATTATCCTGCC  
TCCTTAATAACAGAATATCATTGGATGTGGTGGGTAAATAATATACCCTA  
ACTTTCCTTGCAGAGAGGGGTGGCCAATGAGATGGAAATGAAAGTC  
SG13S73

TGGGATTGAGTTCTTGATTTGATTTTGAGCTTGGCCATCATTGGTGT  
ATAGCAGTGCTAGTGATTTGTGTACATTGATTTTGTAACCTAACACTACTA  
AATTCATTATCAAATCTGGGAGATTTTTGAGGATTCCTTAGGATTTTCTA  
GGTATGAGATCATATCATTGGTAGAGGTAGTTTGAGTTTCTCTTTTCCA[A/  
G]TTTGGATGCCCTTTATTTCTTTCTCTTGCTGATTGCTCTGACTAGGGCTT  
CTAGTACTATGTTGAATAGAAAATGGTGAAAAGTGGGCATCCTTGTCTCATT  
CTAATTTTTAGGGGGAAATGCTTTCAACTTTTCCCCATTCAATTTGATGTTG  
GCTGTGAGTTTGTTCATAGATGATTCTTACTATTTTGAGATATA  
SG13S99

TCTTTTGCCCTGCCTTTCTGCCTTTCTGTCTTTTAATTTGCGGGCTT  
TTGGCAACCACAGCACGGGTCTGGTTTCCTAGGAGTTTCTTTGTAGGATC  
AAACCGCTAGTTGGCTCTTGGCCCTGTGATAGGGCCCTGGGCTAACTTATT  
GGGAAAATGTTGCTGTAACCCCTGCCCAGAGGTGCCTGTGACATGGGC[C/  
T]GCCATCTTCTCCTCTTCCCTTGCTTCAGCCCCACCTAGAAACCTGAACA  
AACATTTTCCTTGACATTTCATAAAGTGTGAGTGGCTCCTCATTTAGCAAA  
ATACATCCCAGGGAAGTTCAAAAGTGAAAAAAGGCCGTAACCTTCTTCTC  
TTCTCAGGGACCTACAGAAAATATGTGGCACCTCGGCAGCCTGGCC  
SG13S382

CATGGATTTTGTTTTCCAAGTGGCAAGATGGCGCCTCCACCTTTGGT  
ATCCTATTTTAGTTCCTGGCAGAAAGAAAGGAACAGGCTAATGGCCCTGA  
TGAGTCTACCCCTTTTAACAGGAGAAAATTTAAAAAACAAAAACCATGA  
AACCTTTTCCCAGAGGCAACAACCAGAATTCCATTTATCTTTCATTGACCA  
[A/G]AACAGACCACATGGTCACTGGTGGTGGCAATGGAGACTGGGGAGAT  
GAATATTTTAAAGGTGGCATATTCCAGAAGAACACTGTGCACTGATTGCAT  
TAATGAACCCATTAATGTGCCAAGGGGAGGTTTACCTATGAGCATGGGCA  
AATTAGAACCCACTCTTGGAGCTGCAGGTGAGCCAATCCCACCTAAACAG  
SG13S383

TGGTGGTGGCAATGGAGACTGGGGAGATGAATATTTTTAAGGTGGC  
ATATTCCAGAAGAACTGTGCACTGATTGCATTAATGAACCCATTAATG  
TGCCAAGGGGAGGTTTACCTATGAGCATGGGCAAATTAGAACCCACTCTT  
GGAGCTGCAGGTGAGCCAATCCCACCTAAACAGTGTGGATGCTACAAGAT  
GG[A/G]GAAGTAAATTGATTCTATTCCATACCCTAACCTCTCTCCAAGATG  
TATTCTTAAATAGAAAGAGGGAAGACAGAAGAAAACATCCAGAATATATT  
TTTATTGTCTTTTACTTCTTCAGTGCATTTTAGATCAGTGCTTCTCAATCTG  
GCAAGGGGCATGCAGGAGGATGTGAGTTTTATCAGGAAAACCTACACAAC  
C

SG13S384

TGAGCCAATCCCACCTAAACAGTGTGGATGCTACAAGATGGGGAA

FIG. 8.6

GTAAATTGATTCTATTCCATACCCTAACCTCTCTCCAAGATGTATTCTTAA  
AATAGAAGAGGGAAGACAGAAGAAAACATCCAGAATATATTTTTATTGTC  
TTTTACTTCTTCAGTGCATTTTAGATCAGTGCTTCTCAATCTGGCAAGGGG  
C[A/G]TGCAGGAGGATGTGAGTTTTATCAGGAAAACCTACACAACCCCCCA  
ACCACAATGCTACCCCCACTCCTGTGGACCTTCTTTAAGAGAGACTCACTA  
TTATAGATGGAGTTGATACGATTTTAAGAGAGGCCATATATTATTGCTTT  
CTGTCTTGAAAACTTGTGATTTTCTGTATTGTGCTACTGCCAAAGAGA  
SG13S381

GGGTTGCAGTGAGCAGAGATCACACCATTGCACTCCAGCCTGGGTG  
GCAGAGCGAGATTCTGTCTAAAAACAACACCGTATTTGGGGCATGCTGA  
TACTAAAAAATTATTCATTGTTTGTCTGAAATTAATAATTGGGGGC  
CCTGTATTTTACTGGGCAACCCATTTGCAATATCAGCAACAATCTCTTATT[  
C/G]AGACCACTGATTAAGTGTGCAAAATTTGAATCTCTGAACAGTACCTA  
TGTCTTGATATCTTAAATTAATGAGTGTCTTAGACACTCAAAGCAGGAGG  
AAGCATTATGGCAGATGTTTGAGCCCCAGAGATGTCCATGAGCACAGCAT  
AGAGCTCAGAGCCTTCTTTATTAATTTGCTTCACGACAGAGCAAAGGACT  
SG13S366

CATTTGCAATATCAGCAACAATCTCTTATTCAGACCACTGATTAAG  
TGTGCAAAATTTGAATCTCTGAACAGTACCTATGTCCTTGATATCTTAAAT  
TAATGAGTGTCTTAGACACTCAAAGCAGGAGGAAGCATTATGGCAGATGT  
TTGAGCCCCAGAGATGTCCATGAGCACAGCATAGAGCTCAGAGCCTTCTT  
T[A/G]TTATTTGCTTCACGACAGAGCAAAGGACTGCAGCAGGTTGACTGAT  
ATAAAAGTTTTACCATGTCTCACAGCAGGCCTTTGCTCAAGTTTCCAGTAA  
GGATATTGTATCATTCTTGCCCTGCAGTACTTGTAATCCACTTACACTGC  
CTGCTGTTGAGTCATTTGTTTCGTCTTGAGTAGCATGTCATCCTTGTTT  
SG13S385

TTGCAGTTCTCATTGCTGGGGAGTCTAAACTGGAATAAAACACCCA  
CTATCTCCATCAGGCTTGCACTAGAGCCCAGCTCTAGCTGGAGAGAAAGA  
AGCTAACCCGCACAGACACAGGACTGTAGGCAGGGAGCATCCGGGGGTA  
TTTGGGTCTGCTGCTGATGTGCCTAAGGCCAACTTCTCTCTGGCCATGCT  
GG[C/T]GTGCATGAGCTCACTAATCTTCCTTTTTGCCTTCCATTTTCTCAA  
TCCTGACTTAGCAAAGGTTGGGCAAAAGAGACTCTGTGTGAGTTTCAGCA  
AAGCCTGAGATGCTGGATTTTCCAAGATACGAGAAGGGGCTGGGGGCTGG  
GTGAACTGGTGGTGGAGGAGGGAAGGATTAATTTCCCAAGGAGGGGAAG  
GG  
SG13S386

GAGAAAGAAGCTAACCCGCACAGACACAGGACTGTAGGCAGGGA  
GCATCCGGGGGTATTTGGGTCCTGGCTCTGATGTGCCTAAGGCCAACTTCT  
CTCTGGCCATGCTGGCGTGCATGAGCTCACTAATCTTCCTTTTTGCCTTCC  
ATTTTCTCCAATCCTGACTTAGCAAAGGTTGGGCAAAAGAGACTCTGTGT  
GA[A/G]TTCGAGCAAAGCCTGAGATGCTGGATTTTCCAAGATACGAGAAG  
GGGCTGGGGGCTGGGTGAACTGGTGGTGGAGGAGGGAAGGATTAATTTCC  
CAAGGAGGGGAAGGGGCCAGGACATCAGGCCCCGGGGACTTTGAAGAGA  
GGGTCGTGGGTAGGAGGTAGATCAAGTGGAGTGACACAAAGGTCAGGAA  
AGAGG  
SG13S1

CATGCCTCCTACAAATTTGACCTGGGCCCAGGGCCATGTTCCGGTGG  
TTTTTAAGAACCGAGGCTCCCAGAAGCAGTATTGGGCAGCTAGAGTGGCC  
CCAGGATCTATATCAAACCTCTACCTGTTTCTGAACCAAATTTCTTCTAGAA  
TTTTATTCCATAAATCTGAATTATGGTGTGAGACTCCTAGCATACACTAAA[

FIG. 8.7

G/T]GAACTCTCTGCCTTGCATTAAATAACAGGAGTTACCCCTGGAGGTAA  
CTCCTAGCCCTGGCTCTTTAGAGAACAGATGCCGAATAGGCATTAGGGGA  
TGTGATGGATGTGCTAACTTTCAAAAAAAAAAAAAAAAAAAGGCCTGAG  
CTGAGTGCTCAGAGATTCACAAAAAGCTGACAGCATCTCTCTGTTCCATTG  
SG13S2

CTTTGGAGCCTGGCAGCCTGGCTTTGAGAACCGGGCTTTAACTTGT  
CACATGACTATGGCCAAGTTCCTGGGGCTCTCCAAGCTTCACTTCCTCTGT  
AAAAAGGGCAATAATATAATACCTGTCTTATTGGGTTTTGTCCATGTTAGA  
TGAGACATTGGGTACAAAGCACTTGGTCCCGTGCCTGGCACATTTACTGC[  
A/G]CTTAATGTATGATAGTTTTCTTATTATTCTAATAAACAATATGGCTTTG  
GGAGTATAGTTCTGCCACATTGCAGTGGCCAGAGTGAAGGTGGTGAGTGC  
CTTCTGGGGCCCTGGGAGTCAAGGTTATCCGCATGCCCTTTCTTGCTTGCT  
CCTCAGTGTGGCTGCCTCTATGTCCACACCATGCAGATGCAACAGGT  
SG13S367

ACATGATCATCCCCTTGGGCTTCTGGTTTTTTTTCTTTCAGGACCTT  
ATTTTCAGGCAAGTGGCCTTTGACCTCTAAGGCTGTCCTTTCCTAGCTACC  
GAATCCAGCATTCAAAGTGATGGAAATATGTATATATAGTAATAGTAAAA  
TATCAGCACTTAATGGCCTGATAAGAATGTCACTGCAATGCTGAGTTTGG[  
A/G]CCAACATTTGCCTGCTCCTGCCATTGAGCCCGGGCTCCCCTCCAGAGC  
TGAGCTGCTGCAAGGGATCTGAGTAACTAGGGCTGTGTCAGAGTGGCGAT  
GACAGCCACCACATGCTAAGGAAGAGATCCCCAAGGACAAGGAGAATCC  
CACGTGGAGCTACTTGCTTCTTTGTCACTCTTGTTTTCTTATTTACAA  
SG13S388

CCGAATCCAGCATTCAAAGTGATGGAAATATGTATATATAGTAATA  
GTAAAATATCAGCACTTAATGGCCTGATAAGAATGTCACTGCAATGCTGA  
GTTTGGACCAACATTTGCCTGCTCCTGCCATTGAGCCCGGGCTCCCCTCCA  
GAGCTGAGCTGCTGCAAGGGATCTGAGTAACTAGGGCTGTGTCAGAGTGG  
C[A/G]ATGACAGCCACCACATGCTAAGGAAGAGATCCCCAAGGACAAGGA  
GAATCCCACGTGGAGCTACTTGCTTCTTTGTCACTCTTGTTTTCTTATTTT  
ACAACCTTCTAAAACACAATCTCTCAACCTCTATTGTTAGCTTGCATTTTT  
CAATCATGAGCACAGCTTTACCTGGCTCCATGCTTTGATTGACTCTACC  
SG13S10

TCTTATTTCAACCTTCTAAAACACAATCTCTCAACCTCTATTGTT  
AGCTTGCATTTTTCAATCATGAGCACAGCTTTACCTGGCTCCATGCTTTGA  
TTGACTCTACCTGCCAACACTGCAACAACAGGGAAAGGGACACCGGCCTC  
ATACCATTAGATGGTGTGTAGCCTGGGCATGAGGATAATTA AAAA ACTCCC[  
A/T]AGGGGATTTTAAACATGTAACACAGTTTGGAAACCATTGATGTAAGAT  
CTTCTTACTCAACATGTGCTCCAAGGAGCTGTTGTATCAGCTTATCAGAAA  
TGTAGATCAGGCCGCACTTGGACCTGTAGAATCAGAATCTGCATTTTATCA  
GATTCCGACATTATTTGTATGAACATTAGCTTTTGAGAAGTGTTGCTT  
SG13S3

CTTTTGACACCAACTACAAGTCAAGGGGTTCCCCAAACCACCCTGA  
GTTGTGATAATTGCTGGGAGATCTGACAGAACTCACTGAAGGTTGTTAT  
ACTCATGGTTGTGATCTCTTATAGGGAGGGAATACAGATTAAAATCAGCC  
AAAGGAAGAAGCACACAGCACAGAGTCCAGGACAGTGCCTGACATGGAG  
CCC[C/T]TACGGTCTCTCCCGTGGAGTCACGGACAGCGCCACTCTCCTGG  
CATTGATGTGTGACAACACACAGGGAGTGTTCCCCACCAGGGAAGCCTTG  
GTGTCCAGGGTCTTTACTGTGGCTCTGTACATGAGCACAGCTGACTGCCC  
ATGCGGCCGATCTGTTCCCAGACTCTCCACCGCTACACATCACTCACAGTC  
C

FIG. 8.8

SG13S368

GTGGCTCACAGAACTCAGGGAAACACAGCTACCAGTTTATTGCGA  
AGGACATTTTAAAGGATAAAAGTAGGCAGATAAAGAGATGCATAGGGCG  
AGGTGTGGAAGGTCCCTAGTGCAGGAGCTTCTGTCCATGTGGAGCGGGG  
GTGCACCACCTCTCAGTACATGAATGAGTTCTCCTTCACCTGCCTATCAG  
CCT[C/T]TACATGTTTACGCTCCCCAACCAGTCCTCTTGGGTTTTTATGGAA  
GCTTCAAGACACCCACATTCTTTCCCCAGAGTATAGGGCAAGACCTTCTCT  
GGGGAGGGTTTTAAGACCCACAGTCAGAAAGGTGGGGTGGGGTCAAGAT  
TAGAGTCCTGCCTTGACGGGCAGGTGAAAGGGGTAGGGGGAGTAGGTGA  
GAA

SG13S369

CGGGGGTGCACCACCCTCTCAGTACATGAATGAGTTCTCCTTCACC  
TGCCTATCAGCCTCTACATGTTTACGCTCCCCAACCAGTCCTCTTGGGTTT  
TTATGGAAGCTTCAAGACACCCACATTCTTTCCCCAGAGTATAGGGCAAG  
ACCTTCTCTGGGGAGGGTTTTAAGACCCACAGTCAGAAAGGTGGGGTGGG  
G[G/T]CAAGATTAGAGTCCTGCCTTGACGGGCAGGTGAAAGGGGTAGGGG  
GAGTAGGTGAGAAAAATTCTGTTTATTTTTTCTTTTTTTTTTGAGACGGAG  
TTTCACTCTTGTTGCCAGGGTGGAGTGCAATGGCACAATCTCAGCTCACT  
GCAACCTCCGCCTCCCAGGTTTAAGCGATTCTCCTGCCTCAGCCTCCCC

SG13S370

ATGAGTTCTCCTTCACCTGCCTATCAGCCTCTACATGTTTACGCTCCC  
CAACCCAGTCCTCTTGGGTTTTTATGGAAGCTTCAAGACACCCACATTCTT  
TCCCCAGAGTATAGGGCAAGACCTTCTCTGGGGAGGGTTTTAAGACCCAC  
AGTCAGAAAGGTGGGGTGGGGTCAAGATTAGAGTCCTGCCTTGACGGGCA  
[A/G]GTGAAAGGGGTAGGGGGAGTAGGTGAGAAAAATTCTGTTTATTTTT  
CTTTTTTTTTTGAGACGGAGTTTCACTCTTGTTGCCAGGGTGGAGTGCA  
ATGGCACAATCTCAGCTCACTGCAACCTCCGCCTCCCAGGTTTAAGCGATT  
CTCCTGCCTCAGCCTCCCGAGTAGCTGGGATTACAGGCGTGTGCCACC

SG13S4

TCTTCATTCCACAAAGCTCAGTGTCAAAACATGGGGTTTACACTGG  
AAGCTGAGGTCACATCAGTAGCCGGGATCAGGGTTCGCCCTAGCTGCCCAA  
TGCAGCTCCCAGGCCTCCTGTAAAACCTTGACCTTTGAGGTCATGACAGCC  
CTCTCCTGCTATGCTCATAGCTGACCACTGAACTCCTGGACACTCCCTCCC[  
G/C]CAAGTTCACAGAGAATGTGGGCACATGCCTTACAGTCTTCCCTTGATC  
CAAATACTGCCTTCATCTTGAGTGACAGCAGCATCTTTTGGATGTCTTGG  
CCTGTCTAGCTTTATTTTTTTGTGTTCTGCCATCAAGTTGCTACTTCTGTTG  
CCATCGTGCCTGTCAGCGCAGTGCAGGCTGTGGTGAAATCCCACGA

SG13S5

TATTTTTTTGTGTTCTGCCATCAAGTTGCTACTTCTGTTGCCATCGTG  
CCTGTCAGCGCAGTGCAGGCTGTGGTGAAATCCCACGAACTCAGGCATCA  
CACTGACCGGGTCTGAGTCCTGTCTCAGTTGTCAGCTAGTTGTGCAATGAA  
GGGAAAGGGACCTACACTTTCCAAGCCTCAATTCATCTATGGCAT[G  
/T]GTGACAATAATGGAGGTTGATTTAAAGTCCTTTGTAAGAATTAAGAGTT  
ATAATAGACATAAAGTGCTGTATCTGGTATACCTAGAAAACATTCCATAA  
AAGTTAGTAATTGTTGGTCAATGTAATGATGACTCTCTAGGCTAGGATTCA  
GCTTCATTGCATGCACATGGTGCACCTCACAGGGCGTGACCTCTCTCT

SG13S389

GGTATACCTAGAAAACATTCCATAAAAGTTAGTAATTGTTGGTCAT  
GTAATGATGACTCTCTAGGCTAGGATTTTACGCTTCATTGCATGCACATGGT  
GCACTCACAGGGCGTGACCTCTCTCTGTCTCAGTAACCTCATCTGAGGACC

FIG. 8.9

GGGATAATCATACCGCTTCAAAGGGATGTCATAAAGATTAAATAATATGT[  
A/G]TAAGGCTGCTTGCAATTTAGCTGCATTCAACAAATATTTCTGTATCTTT  
CTCCTCATTTCTCCTTACTTTCTTGCTTATTATCTGCTCTAGGTATAGATTTC  
AGAGAACTAAGCTTGTTACAATCCTTCATAAAATAACCAGGTTGGTTAGG  
GCATTTCCAAGAGTCAATACTGTTTAGTGACTATTCTCTGTTTAAT  
SG13S90

AAGGCTGCTTGCAATTTAGCTGCATTCAACAAATATTTCTGTATCTTT  
CTCCTCATTTCTCCTTACTTTCTTGCTTATTATCTGCTCTAGGTATAGATTTC  
AGAGAACTAAGCTTGTTACAATCCTTCATAAAATAACCAGGTTGGTTAGG  
GCATTTCCAAGAGTCAATACTGTTTAGTGACTATTCTCTGTTTAATCT[A/C]  
TTTTGATTGTCCAGGGTCATCTTTTGCTATGTCATAGGTTGTTGGCTTCTTC  
TAGAGAAGTGAGACGATGGACAAGTTCCAAGTGAGTGAGGCGACTGGTC  
AGGATATTCCGCTGAAAACTCATGTCAGTTCTAATTCGTGATTGTAATTC  
AATCACAGCCTGAGAACAGTAGGACTGTAGTTCAAATGCTCTGTT  
SG13S390

CCTGGGTTCAAGCAATTCTCCTGCCTCAGCCTCCCAAGTAGCTGGG  
ACTACAGGCACATGCCACCACGCCCAGATAATTTTCGTATTTTLAGTAGAG  
ACGGGGTTTCCCCTTGTTGGCCAGGGTGGTCTTGATCTCTTGACCTCATGA  
TCCGCCCACCTCGGCCTCCCAAAGTGCTGGGATTACAGGCGTGAGCCACC[  
A/G]CGCCCGGCCTCTAGAGGATAATTTTAAATGTGCTTTTGCATTTGGAA  
AATGTGATTGGCATTTTTTTCTAATTTTCTAATATGATACGCTGTCGGATGC  
TATGGATTACTTAAACCCTCTGGCTACCTAGAAAGATCTTTAAGTGGTTCT  
CAACAAGCTTCATACGCAATGTAAATTGTATTATCTCTCAGGATGT  
SG13S6

TGTGATTGGCATTTTTTTCTAATTTTCTAATATGATACGCTGTCGGA  
TGCTATGGATTACTTAAACCCTCTGGCTACCTAGAAAGATCTTTAAGTGGT  
TCTCAACAAGCTTCATACGCAATGTAAATTGTATTATCTCTCAGGATGTGT  
GAGAACATCTGTTTTTCTTCTAATGCAGTAAACATATAAGGGTCTCTTG[A/  
G]GATATCTTTTAAATAGACTTAATACAACATTCAGGAATGATAACAAAAT  
ATAATCACAGTTGTAAGGGAATGTGAGCATTTCATATTAATAACATTGGA  
ACCTTATGTTTAATACAGTGTTAAAAGTTGACAAACATGTAGGAGTCAGA  
AAATTCAATTAAATTATCACAGTAATATGAATTTAGCCACATCCTGT  
SG13S391

ACTTAAACCCTCTGGCTACCTAGAAAGATCTTTAAGTGGTTCTCAA  
CAAGCTTCATACGCAATGTAAATTGTATTATCTCTCAGGATGTGTGAGAAC  
ATCTGTTTTTCTTCTAATGCAGTAAACATATAAGGGTCTCTTGGGATATCT  
TTTAAATAGACTTAATACAACATTCAGGAATGATAACAAAATATAATCAC[  
A/G]GTTGTAAGGGAATGTGAGCATTTCATATTAATAACATTGGAACCTTAT  
GTTAATACAGTGTTAAAAGTTGACAAACATGTAGGAGTCAGAAAATTCA  
ATTAAAATTATCACAGTAATATGAATTTAGCCACATCCTGTGTTAGTTATG  
AAATCCATTTAACACCACAAACAGTAATATTTTATAGCCAGTTTATTCA  
SG13S392

CATTTAACACCACAAACAGTAATATTTTATAGCCAGTTTATTCAAAA  
GGAAAACAGGAACTAAACCACTTTTCATGCAATATATACTCTGTTAATGTG  
GTCAGGCTAATTTTGCTGGGGGAAGGAACCTTAACCTTTGAATATTTGAATG  
CCCAGTCATTTAATCTGAATATCCTATTTTCTTGCTGTTGCAAAAATTTTT[  
G/T]TCAATAAAAGGCAGAAAAAGAAATCTCTTCTCCATGCTCATCCCTAA  
GAGAATGGGTGTCTGTACCCTGAGAGCATTATGAGAGGGGACAACCAC  
TTTTCTAATTTTCTTCCCACTTCTCTGTGGGCACAAATGCTCTTTGGTTGA  
AAGAGTTGTAATTCAGTCCCAAGATGAGGTGTGGTTACTGCATCCCTA

FIG. 8.10



SG13S371

TCAATCCATGCTCCACACTGCAGCCAGAGTGCTCTACAATGCAAAT  
CCATTTGTGAGACTCCTCCTCTTAAATCCTCAAGTGGCTTCTCTTTGCCCC  
CAGGATCATTTTGAACCTCTTAATGGAAGAGGCATGGCCCTTTGGGATG  
TGGTTCCCCAACCCCTCCCACATCATCTTTTCAATCAGATTTCCTACTAA[A  
/G]TGGAAATTTTTTCAGGTCCTCAACTTTATGGTGACTTTCTCTTGCTCAGG  
ATCTTTGAACATACTGTTTCTTCTTTCCTTTTGTATTTGCCAAGACAACACT  
TCCTCTGGTAAGATTTTCCTGACATCCTCTATAAAAAAAGATTGAGATAGT  
TGACTACCCAAAATGTTTCCCATTCATTCCAAGCTCTATTCAAG

SG13S372

AACACTTCCTCTGGTAAGATTTTCCTGACATCCTCTATAAAAAAAG  
ATTGAGATAGTTGACTACCCAAAATGTTTCCCATTCATTCCAAGCTCTATT  
CAAGGCAGTAAAGTGCCCGGCTGACAGATTGCATTCTCTCATCTTTTCTGAA  
GCTAGCAATGGCCATGCAACAGCATTCTGGCCAATAAGATAGAAGTCGAA  
[A/G]TTGAAGGGTGGGATTTCCAAGAAAGCTCGTTGAAGACATAATTCCTC  
ATTTCACTTCTTACTCTTTCTCTTTCCTGCTTCCTAAAAATGCGGTGCAGATG  
GCAGACACTTCAAAGCTGTCTCAGGCAATCAGGTGATGTAAAGGCAGAAA  
CCAGCTTTATGATGGGTAGAACAGGAAGAAAGAAGGCACCTATGTTCT

SG13S393

CCTACAAATCTCATGTTGACATTTTATCCCTAATATTTGGAGGCAGG  
GCCTAGTAGGAGGTGTTTTGGTCATAGTGATAAATGGCTTGGTGCCGTTCT  
CACAGTAACGAGTGAGTTTTTATTCTAGTGGTTCCTGCAAGAACTGATTGT  
TAAAGAGCTTGGATCCTTCCACCCCTCTCTCACTCTTGCTTCCTCTCTC[A/  
T]CACCTTGTAATCTCTACAAGCTCTTCACCTCCCCCTTCTCCTTTTGCCATA  
AGTGAAGATTTCTGAGGCCTCACCAGAAGCAGATGTTGGTTCCATGCTT  
CTTGTAACAGCCTGCAGAACCATGAGCCAAATCAACTTCTTTTCTTTATAAT  
TATCCAGTCTCAGGTATTCTTTATAGCAACACAAATGGACTAAGA

SG13S373

GTTGTTTTCCAGCTTTGAACTATTTTGAATCCTAAAAGACTGCCAGTT  
TTGAATGAGACCCCAAGACAATGAATGTAGGCTCTGTATACAAGTTCAGG  
CTGCTGGGCAACTTAGGCCTTAAGACACAACCTCTGCCACTTAGGCCTTAA  
GACACAACCTGACATGATGGTGCTTAAAGTGGCTGTGATGGAAAAGGAGG  
CT[A/G]TTTGAGGCCTTTGGAGTGCTTTTATAGGTGAACCCCAAGCATAGCA  
CCTAATGATTTGGAGCAAAGCTGTGTCATTCCCCAAAGATAACTATTCGCC  
TTTTGAGAAACATCTTCTAGCTACTATCAATAATAAACACAGAATGCATC  
ACCATGGGCCACCGTGTGTCTTTTGACCTGAGTTTCCATTGTGAACAAGA

SG13S374

AACTCTGCCACTTAGGCCTTAAGACACAACCTGACATGATGGTGCTT  
AAAGTGGCTGTGATGGAAAAGGAGGCTGTTTGGAGCCTTTGGAGTGCCTT  
TATAGGTGAACCCCAAGCATAGCACCTAATGATTTGGAGCAAAGCTGTGTC  
ATTCCCCAAAGATAACTATTCGCCTTTTGAGAAACATCTTCTAGCTACTAT  
C[A/G]ATAATAAACACAGAATGCATCACCATGGGCCACCGTGTGTCTTTT  
GACCTGAGTTTCCATTGTGAACAAGAGTCATTTGATCCAAGGCAGAAAGT  
TGGGTGCACACAGCAGTGTTCATCATCAAATGGAATATGAGATTGGGCC  
CAAGTAGGTCCTGCAGACACAAATAAGTTGCAAGAGCAAGTAGTACAGG  
CG

SG13S375

GAAAAGGAGGCTGTTTGGAGCCTTTGGAGTGCCTTTATAGGTGAAC  
CCCAGCATAGCACCTAATGATTTGGAGCAAAGCTGTGTCATTCCCCAAAG  
ATAACTATTCGCCTTTTGAGAAACATCTTCTAGCTACTATCAATAATAAAC

FIG. 8.11

ACAGAATGCATCACCATGGGCCACCGTGTGTCTTTTGACCTGAGTTTCCA  
[C/T]TGTGAACAAGAGTCATTTGATCCAAGGCAGAAAGTTGGGTGCACAC  
AGCAGTGTTCATCATCAAATGGAATATGAGATTGGGCCCAAGTAGGTCC  
TGCAGACACAAATAAGTTGCAAGAGCAAGTAGTACAGGCGCTTGGCCTGG  
CCAGTACTGTTGCCAAGTTGACTGCTTCCCCTCAGTCTGCATCTGTGGCTT  
SG13S376

CCCCAAAGATAACTATTCGCCTTTTGAGAAACATCTTCTAGCTACT  
ATCAATAATAAACACAGAATGCATCACCATGGGCCACCGTGTGTCTTTT  
GACCTGAGTTTCCATTGTGAACAAGAGTCATTTGATCCAAGGCAGAAAGT  
TGGGTGCACACAGCAGTGTTCATCATCAAATGGAATATGAGATTGGGCC  
CA[A/G]GTAGGTCCTGCAGACACAAATAAGTTGCAAGAGCAAGTAGTACA  
GGCGCTTGGCCTGGCCAGTACTGTTGCCAAGTTGACTGCTTCCCCTCAGTC  
TGCATCTGTGGCTTCATGGGGAGTTTCTATGACCACTTGATGGAGGAAA  
AAACAAATTGGAGCATAGTTTATAGTGCTGGTACTACCCAAAGTGGCTAG  
CT  
SG13S394

GTCCGTGAGTTACAGATCTACACAAAATCACAGAGAGTGGTTAATC  
GTTTAGTCTGATGGTCAGGGACTTCCAAGAGACATGATTAGAAAACCTGGT  
GACAAGGAGTCCTGGGGAAGAGGCATATGGATACCTCTGAACACACACA  
AAACATGAGAATATGTATCCCATATGAATGTAAACCAAGAGCAGCCACA  
ACA[C/G]AAGAGGATTTTAAAATCAGCTGAATAAGATGATTCTTGACA  
GCATCAGCTAGTCTCTTTCCCCAGCCACTGTTGCCCAGTGGGCTTACATAT  
ATCATGGCCATGGGGGCAGGGCTATGTATGGACACAGCAACATGAATTTT  
CACTCATCAAGGCCAATTTGGCTCCAGCCATTGCTGAGTGCTCAGCCTGCC  
A

SG13S25

ACATGATTAGAAAACCTGGTGACAAGGAGTCCTGGGGAAGAGGCAT  
ATGGATACCTCTGAACACACACAAAACATGAGAATATGTATCCCATATGA  
ATGTTAACCAAGAGCAGCCACAACAGAAGAGGATTTTAAAATCAGCTG  
AATAAGATGATTCTTCTGACAGCATCAGCTAGTCTCTTTCCCCAGCCACT  
GTT[A/G]CCCAGTGGGCTTACATATATCATGGCCATGGGGGCAGGGCTATG  
TATGGACACAGCAACATGAATTTCCACTCATCAAGGCCAATTTGGCTCCA  
GCCATTGCTGAGTGCTCAGCCTGCCAAGATAGAAATCTACGCCAATATGG  
CACCATTCCCTGGGCTAGAAAACCAACTGGTGGAAGGTTGATTACATTGG  
ACC

SG13S395

GGGAATACAATGGTGGTTCCTAACTGACAGCTGAGTTTGCCAT  
CTCCTCGTGCCAGTGAATACACAAGCAAGGAAGGGGGTTCCTTTCTCACC  
TAGGGTGACTGATCCTAATTACCAAGGAGAAATTGGACTGCCACTTCACA  
ATGAGGGTGAGGAGTATGTACTCTATGTGTCTGTGATTAATGTCAATAGA  
AA[A/G]TGACACCAACCTAGTACACAGAGGACTGATCATGGTCCAGGCCC  
TTCAGGAATGAAGATTTGAGTCACCAGGCAAGGAACCTGGACTCACTGAG  
GAGGGCATATTCCAAGGAGAATATTTTATCTATGTCCATCTATGTCCATCT  
ATATTCCATCTGTGTTCCCCTTGGAATTCCTATTCATGAACATGGGGAATT  
C

SG13S396

TATAGAATGAGTAGTGGAAGGTAGTTATAAATGTAAGTCAAAAAC  
CACACAACCAATTTGAGAAATGAGGAAGGTAATAGTGTTGAATATGTCTT  
CTTTATCTTGATATAAATGTATTTGTGCATATATTAACCAGTTTATTTATTT  
ATTATTATTTTTTGAGATGAGCTCTCGCCATGTTGCCCAGGCTGGTCTTGA[

FIG. 8.12

A/C]CTCCTGGGCTCAACTGATTCTACCATTTAGTCCTCCGAGTAGCTGGGA  
CTACAGGCATGCACCACCATACCAGCTGACCAGTTTTTTCCTATTCCTCT  
ACTTAATTTCTCTACTATAACAATAATATGTGTTAATGGTAGTTAACTTT  
ATATCTCAGTATTAAGTCACAAGATATCAAAAAGGGAATGCGACTTA  
SG13S397

ATGTCTTCTTTATCTTGATATAAATGTATTTGTGCATATATTAACCA  
GTTTATTTATTTATTATTATTTTTTGAGATGAGCTCTCGCCATGTTGCCAG  
GCTGGTCTTGAACCTCTGGGCTCAACTGATTCTACCATTTAGTCCTCCGAG  
TAGCTGGGACTACAGGCATGCACCACCATACCAGCTGACCAGTTTTT[C/T  
]CCTATTCCTCTACTTAATTTCTCTACTATAACAATAATATGTGTTAATGG  
TAGTTAACTTTATATCTCAGTATTAAGTCACAAGATATCAAAAAGGGAAT  
GCGACTTAGTTACAAGCAGAATGAATATCACTCAAAGATGAATAAAGAG  
AAGAGGGTAGTGCATTTTCTGTTGGATGAGAGAAAGTTTCATTGTT  
SG13S377

GCAGTGGCGTGATCCCAGCTCACTGCAATCTCTGCCTCCTGGGTTT  
AAGTGATTCTCCTGCCTCAGCCTCCCGAGGGGCTGGGATTGTAGGCGTG  
ACCACTATGCCCATCTAATTTTTGTATTTTAGTAGAGATAGGGTTTTGCC  
ATTTTGGCCAGACTGTCTTGAACCTCCTGACCTCAGGTGATCTGCCTGCCTC[  
A/G]GCCTCCACAGTTTTGTGATTATAGGCATGAGCCACCGTGCCCGGCCT  
TAACCTTTGTTTTCTTACACAACACACTACGTGATGTTTTCCACATGCATG  
GGTCATTTGCTTCATTTACGTACAAATGCATAAGCAATATACTGTGTGGTG  
TGAGTTTGTGATGGGAAAAGGAAGAAGTTTTGCGGATACTACACTGG  
SG13S189

GCCAGGCTGTTCTCCAACTCCTGGACTCAAGCCATCCTCTAGCCT  
CGGCCTTCCAAAGTGCTGGGACTATAGGCGTGAGCCACGGTGCCAGGCCC  
TTGACCACATTTTAAACCCCTCTGAACCTCAGTTTCACTTTCTGGGCAATG  
GGAGGGGGGTAATTTGTCCCTCAGAGGGTTGCACTGAGGGGGCAAATGTGA  
G[C/G]CTCTGGGTACAATGCCAGTACAGACTAGGTCCCCACGACACAGCC  
GCTCAGCGGCTCCGGATTCTGGGCTGCTCTGGACTGCGGCCAGGCGGTCT  
TCTGCGGAATCCGGGCAGGCAGGGCGGGCTGCGCTCCCCTCCCCGGCTC  
TCCCGGTGCCCTTGTCTTTTTGTTCTGTCTCAGCAGCTCTCTATTAAGAT  
SG13S100

TTTTTGTCTGTCTCAGCAGCTCTCTATTAAGATGAATGGCATTTC  
AAAGGCTTCACCTCTGATAAGTGTTCCTCTGCAGCTGCAGCCAGAATCTTA  
ATGTGCGCGCTGTAATTTAATGGCCGTCTCGGCTATTAACACGCTCTTCTC  
GGGTGAAGTGGAATCCCTCCATCCCCGGGCCTCTGCACGTGCTCTGCGC[A/  
G]CTGGCTGGGGGTGACTCCAAGGAGCTCAGAGCGGGGTGCCCGGCACCT  
CTCGCCAGGCGCCTTTCGACCTTCTAAAGCGCGAATGGCTGGACTTTTCTC  
CCATGTGTGGGGCCCCAGAAGGTGTGGGGCCCCAGAAGGTGTGGGGTCCC  
TGCGTTCCACGGAGCCCGGAAGGTTTCCAGTGATGGTGGGGGCTGACC  
SG13S398

GGAGCCCGGAAGGTTTCCAGTGATGGTGGGGGCTGACCACGTTGG  
TCCCGTGGGTGCTGTTTTCATGTGCCGGCAGATTGGGATGAGTTTAAAAG  
ACAGAAGCGTGTAGGATAGAGAACTTCTTTAAAAACTGGAAATTTTAAT  
CTGGGGATTATAACTATTGGACAGTCAAGTGCAAGAGTGAATACACTTCT  
CA[C/G]TCCCTCCTCCCAATTTTTATTTGCGGGATTAGTCAGTCCCCCTCTG  
CCACATGATAATTGTGAGAACTACCAGGGTCTTCATTCTCCTGCCATCTGG  
TTGACCTCTCCAAGAATGGACACCCGGGCAGCCTGGGCCAATGAGGCTGT  
CCTAAGAGTTTAGATGAGAGAAGTCAGTCTTTGACAGGTGATGGAAGCTG

FIG. 8.13

SG13S94

CAGTGATGGTGGGGGCTGACCACGTTGGTCCCCGTGGGTGCTGTTT  
TCATGTGCCGGCAGATTGGGATGAGTTTAAAAGACAGAAGCGTGTAGGAT  
AGAGAAACTTCTTTAAAACTGGAAATTTAATCTGGGGATTATAACTATT  
GGACAGTCAAGTGCAAGAGTGAATACACTTCTCACTCCCTCCTCCCAATTT  
[C/T]TATTTGCGGGATTAGTCAGTCCCCCTCTGCCACATGATAATTGTGAG  
AACTACCAGGGTCTTCAATTCTCCTGCCATCTGGTTGACCTCTCCAAGAATG  
GACACCCGGGCAGCCTGGGCCAATGAGGCTGTCCTAAGAGTTTAGATGAG  
AGAAGTCAGTCTTTGACAGGTGATGGAAGCTGTAAAATGTAAAACCTCCA  
SG13S101

TAAGAGAAGCTGAGAGAGAGCGAGAGGAGAGATTGGAAGAAAGA  
CAGAGACAGAGGTAGAGAGAAGGGAAAGAGAGAGAGAAAAGGGACAGAA  
GAGAGAGAAAAAAGAGGGGGCCGGGCGCGGTGGCTCACGCCTGTAATCT  
CAGCACTTTGGGAGGCCGAGGCGGGCAGATCACGAGGTCAGGAGATCGA  
GACCATCC[C/T]GGCTAACACGGTGAACCCCCGTCTCTACTAAAAAATAT  
AAAAAAAATTAGCCAGGCGTGGTGGTGGGTGCCTGTAGTCCCAGCTACTG  
AGGAGGCTGAGACAGGAGAATGGCGTGAACCCGGGAGGCAGAGCTTGCA  
GTGAGCTGAGATCGCGCCACTGCACTCCAGCCTGGGCAACAGAGCAAGAC  
TCCGTCTCA

SG13S95

TCCACCAGCAGCTTTTCTGAGTCTCCAGCTTGCAGATGGCAAACCA  
TGAAACTTCATGGTGTCCATGAGCATGTGAACCAATTTCTATTATAAATCT  
GCAATATATATATATGAGGAGACTTATTTATATATTGGTTCAGTTTCTCTG  
GAGAGCCTTGGCTAATATAAAGTCTATACTCTACAAAGTGCCCTAGGTAC[  
G/T]CAGGGAGTACCCAAGTGTGTCATGACCAGCCCGACAGCCCTGGCTGC  
TGGCTTCCCCGCACAACTCTGCACGCTGCCTTCATCAGCCTTTCTCTCT  
CAGCTGAACCGAGGGCATTGAAGCGGGCCTCTGGCACTGTACCTATGAGG  
GAGCAATATCTTCCCCTACACTGACCTCTTCCGTGCCGAGATGCAGCCC  
SG13S102

GCCTCTGGCACTGTACCTATGAGGGAGCAATATCTTCCCCTACACT  
GACCTCTTCCGTGCCGAGATGCAGCCCTCCCTGCTGCCACTAGTTACAGTG  
GTCCATGTTCCCTTTCAAAGTGAAGTTTTGATAAAAGCACCTCTTAACCAA  
TGCCAAATAGCTAAGTCTGGGACAAAGATTGCAGGTATTTTGCATTTTCC[  
A/T]TGTAACCTCAGAGGGATTGCCATTCACTGATCTGAGCTGCAGAAT  
ACCAGGCAGCCACCTCACCCACCCAGCAGGTCCACTCTTATACTTTCTCAG  
AAAGCACAGCCACTCTACTCTTATTCAGTTGAAAAGAATTTCCAGGAAGG  
TGTTTCTGCGATTGCCTCAGAAAAGTCAGTTCCCTTTGGGAATTTCCCT  
SG13S103

TACTTTTCTCTGAAGAAATGGAGATATCAGCTGTCCCTCCCCACTG  
CCATTTATTCCTTCCTTCATTCAAACCTTATGTGGCTGCTACTTACCGTGTG  
TTAAGTGTTCAGTCTTTTTTCTTGGAATTCAAAAAAAGAAGGACAGTATTTG  
GGGCACAGATCTTTTGGTGTCTATACATTTTTTTAAAGTTTCATTTTA[C/T]  
ATTTGTGTGTGCGTGTGTGTGTGTGTGTGAGACAGTCTTGCTCTGTTGCC  
AGGCTGGAGTGCAGTGGCATAATCATTTGGCTCACTGTAGCCTCAAAGTCC  
TGGGCCCAAGCAATCTTCCCACCTCAGCCACCCAAAATGCTGGGGTTACA  
GGTTTATGCCACTCTGTCTGACCTGAAAGTTTTGGGTTTACTTTCC  
SG13S104

GCATAATCATTGGCTCACTGTAGCCTCAAAGTCCTGGGCCCAAGCA  
ATCTTCCCACCTCAGCCACCCAAAATGCTGGGGTTACAGGTTTATGCCACT  
CTGTCTGACCTGAAAGTTTTGGGTTTACTTTCCCTTCTTTCTTTGCTGAA

FIG. 8.14

GTCAGAGATGATGGCAGCTTCCAGATTCTCTGGTGCCTGTGCTGGGCTC[A/  
G]TGCTGGTCATGGTCTTGGGTCCAGGATTCATTCTGGAGACTCTCAGGGA  
AGTTTCCCATGACAAGGAAATGTAGGAGAGTGTGCTGGCTTTGCGTGCTC  
CTCTGCCAAGCCCTGCTTCTCCTGGTGGGACACACTGAACCACAGCCAGG  
GCATTTTGGTGGTTAGTTAAAAAAAAAAAAAAAAAAAAAAAAAAGGAAG  
SG13S191

CTTCAGAAATTGTAATGATGAAAGAGTGCAAGCTCTCACTTCCCCT  
TCCTGTACAGGGCAGGTTGTGCAGCTGGAGGCAGAGCAGTCCTCTCTGGG  
GAGCCTGAAGCAAACATGGATCAAGAACTGTAGGCAATGTTGTCTGT  
GGCCATCGTCACCCTCATCAGCGTGGTCCAGAATGGTAAGGAAAGCCCTT  
CA[A/C]TCAGGGAAGAACAGAAGGGGAGATTTTCTTTGATGGTTGTTTGGGA  
AGTCAGGCTTAAACAATTGTGTCTGTGTGTGCGCATGCACAAACACTTTTA  
CCTTATCTTTATTTTCTTCTTTTATTTGAATGTATAGGGTTGTGTGTATTTT  
TGTGTAAATTTGGGGTTTTCTCTCTTAGTCTTTCACTTTTGTGGTG  
SG13S105

TTTTCTAACATCTGCAGTGCAATTGAAGTTACCAGTCATCTGCAGTC  
TAAAAAGAAAGTGATTTTGGGAGGTGCGTAGAAAAAATCATCTTATTATT  
TTTCTCTATATTACTTTTTTCTTTTTTCTCCTGAAGAACTTTTTTTTTTG  
GTGATACCTTCTTTTTCTCTAGCACGTATAATTTTGGGAAGCATTTTTC[A/G]  
TATGCAGTGTATACTTCAGAAAGAGAGAGAGAGAGAGAGGAAAAATTGTCCTG  
TTCAGCGTTTGCATTTCCATTATTCCTGCTATTAGTTAAAAACAACAACAA  
CAACAAAAACAAGCAGGATACCTAGATCTGGAAAAGGGAGAATTGTGT  
AGAGCTGTCTTCCTAAAGTTCTGAGTTAGGGCTGCCTCAGACCACTT  
SG13S106

TTTTGGAAGCATTTTTTCATATGCAGTGTATACTTCAGAAAGAGAGA  
GAGAGAGAGGAAAAATGTCTTGTTCAGCGTTTGCATTTCCATTATTCCTGC  
TATTAGTTAAAAACAACAACAACAAAAACAAGCAGGATACCTAGA  
TCTGGAAAAGGGAGAATTGTGTAGAGCTGTCTTCCTAAAGTTCTGAGTTA  
GG[A/G]CTGCCTCAGACCACTTTCATAACTATCTCCAGTGGCTTTGTGTTTT  
ATATTTATTAAGATAGAGAAAAAAGAGTAATTACTAAGGGCAGCTGCTG  
TAGCTTTATGGTGATTACTGAACATTGACATGCTGTACGTTTTTGGAACT  
TTGAGTATTTAATCACTTTGGGATATTCTATTTTCCCCCATCTTGAGTGT  
SG13S107

GGAACCTTGAGTATTTAATCACTTTGGGATATTCTATTTTCCCCCAT  
CTTGAGTGTGGACAGATGCTGGTGTAGTGCCTTCTGGGCACAGAGCAAG  
CCTCCCCCTCAGCCTCTGCACCAGAAAGGCTCAGCTTCACACACTCCAAGT  
ATGTTTTCTACAAGAACTACACTTTGTGGCTTTCTGACCCAAACATTTTT[A/  
G]TACTAAATTACACACAACAAAGTTGTAGCTCAGAGAGGGAACAAATGG  
CTTATTTAGGCCACCATTTTCTTGAGCCATTATGATTTACACAGGGCTCC  
CTTGCCCTGTAAATTGGCAAGGATTCCATTATTCAACCCGCATACATGTA  
CAGAGACCCTGCTCTGGCCCAGATAGTATTCTGGGTACAGGCGGATA  
SG13S108

TGTGGACAGATGCTGGTGTAGTGCCTTCTGGGCACAGAGCAAGCC  
TCCCCCTCAGCCTCTGCACCAGAAAGGCTCAGCTTCACACACTCCAAGTAT  
GTTTTCTACAAGAACTACACTTTGTGGCTTTCTGACCCAAACATTTTTATA  
CTAAATTACACACAACAAAGTTGTAGCTCAGAGAGGGAACAAATGGCTTA  
[C/T]TAGGCCACCATTTTCTTGAGCCATTATGATTTACACAGGGCTCCCT  
TGGCCCTGTAAATTGGCAAGGATTCCATTATTCAACCCGCATACATGTACA  
GAGACCCTGCTCTGGCCCAGATAGTATTCTGGGTACAGGCGGATAGAGCA  
GGAACAAAAACAGCTACAGTGATGGACAGGTCAGCCTGCAGCAATGCC

FIG. 8.15

SG13S109

TTTTTATACTAAATTACACACAACAAAGTTGTAGCTCAGAGAGGGA  
ACAAATGGCTTATTTAGGCCACCATTTTCTTGAGCCATTATGATTTACAC  
AGGGCTCCCTTGGCCCTGTAAATTGGCAAGGATTCCATTATTCAACCCGCA  
TACATGTACAGAGACCCTGCTCTGGCCCAGATAGTATTCTGGGTACAGGC[  
A/G]GATAGAGCAGGAAACAAAACAGCTACAGTGATGGACAGGTCAGCCT  
GCAGCAATGCCTGCAGTCTCTGCAAAGGTAGCTGTATGGGTGGGCAGGTG  
GCTAGCACTTATTCAGCTCTGGAAGGATCTCCCCTCTGGCCTCTCCCCTGA  
CACCCATCAATAAAACTGAGGAGCATCGGTGGACAGGGGACCTTGTGCCC  
SG13S110

TTTTCTTGAGCCATTATGATTTACACAGGGCTCCCTTGGCCCTGTA  
AATTGGCAAGGATTCCATTATTCAACCCGCATACATGTACAGAGACCCTG  
CTCTGGCCCAGATAGTATTCTGGGTACAGGCGGATAGAGCAGGAAACAAA  
ACAGCTACAGTGATGGACAGGTCAGCCTGCAGCAATGCCTGCAGTCTCTG  
C[A/G]AAGGTAGCTGTATGGGTGGGCAGGTGGCTAGCACTTATTCAGCTCT  
GGAAGGATCTCCCCTCTGGCCTCTCCCCTGACACCCATCAATAAAACTGA  
GGAGCATCGGTGGACAGGGGACCTTGTGCCCCCTCCCTGCCTGTGCAGTT  
GGGGCTGAACCCAGCTACGAAGTTTGAGCTCACTCTCTCCAGCTCCCTCTC  
SG13S111

GACAGGTCAGCCTGCAGCAATGCCTGCAGTCTCTGCAAAGGTAGCT  
GTATGGGTGGGCAGGTGGCTAGCACTTATTCAGCTCTGGAAGGATCTCCC  
CTCTGGCCTCTCCCCTGACACCCATCAATAAAACTGAGGAGCATCGGTGG  
ACAGGGGACCTTGTGCCCCCTCCCTGCCTGTGCAGTTGGGGCTGAACCCA  
GC[C/T]ACGAAGTTTGAGCTCACTCTCTCCAGCTCCCTCTCAATTCAGAGCT  
GAACTGTGGGAAGCTTCAGAGCTCTCTGTTTCAAGGACAGGTTCTCCTCAC  
CTCTCCTAATGGAGGTGCACCAGGGAAGTGGCCCTGCTCTGCCCAGGGCT  
TTCTCCTGGACTTTGCCATCATGGTCTAGCAAACCCTGTTTCAGATTGAGG  
SG13S112

CACTCTCTCCAGCTCCCTCTCAATTCAGAGCTGAACTGTGGGAAGC  
TTCAGAGCTCTCTGTTTCAAGGACAGGTTCTCCTCACCTCTCCTAATGGAG  
GTGCACCAGGGAAGTGGCCCTGCTCTGCCCAGGGCTTTCTCCTGGACTTTG  
CCATCATGGTCTAGCAAACCCTGTTTCAGATTGAGGTGAGTGGTGAGATT[  
C/T]GAATTCTTTTTGACAGATAGGATTAAGTCTTCTTCTGTGGGACAAGTG  
GGAGGTAGAGGTAAGATTAAAGATGGCCAAATGTCTGAGTCCTGACAGCC  
ACAATATGGAGATCTAGACTTTTTACAGACCACAGGGCACAGGGGCCTCA  
CTAACAGAGTTCCCGGAAGTGATGAGTGTGCTGGGGGCTTCTGTTGA  
SG13S113

TAGGATTAAGTCTTCTTCTGTGGGACAAGTGGGAGGTAGAGGTAAG  
ATTAAAGATGGCCAAATGTCTGAGTCCTGACAGCCACAATATGGAGATCT  
AGACTTTTTACAGACCACAGGGCACAGGGGCCTCACTAACAGAGTTCCCG  
GAAGTGATGAGTGTGCTGGGGGCTTCTGTTGAAGAGACACTAGAATGG  
AC[C/G]AGCTGGGAGCTAATTTTTTGGGCTGGAGTGTGATGGCCTGCACAT  
CACTGCCTCTGTCCCTCCATTGTACAGCTGCCCTTAGGAGCCAGCTGAG  
GCAATTTGTGGTCAGAGTGACTTTGCACAGTTGTCTGCCTGTGTTTCAGGA  
AGGGAGTTTCTGTGGTCCCTTTGAAACCACAGAAGAGCCCCCTCGTATAGC  
SG13S114

AGTTGTCCTGCCTGTGTTTCAGGAAGGGAGTTTCTGTGGTCCCTTTGA  
AACCACAGAAGAGCCCCTCGTATAGCTCTCAATGGAGGGGGCAAACATT  
CAAATAACTCAGGAGATAACACAACCTATTTGTTTTTAAGTGTGAGTTTTTA  
GGCAATCACAAAGATCCAGATGTATGTCCAAGCCTCTCTTTGCAATTCTA[

FIG. 8.16

A/T]TTAACCTCAATGTTGCAACCATAGACCTACCTTACAGAGTTCAAAAA  
AATATGCAAAAACCTGCCTTTCTTCTTCCTCATACCCCAAATGCCATTC  
TGAACATTTCTGTAGTTAAAAAAGATTTCCATGGTGTACCAGGCACT  
GTACACAGTCTGTGTCCCAAGACAAGGAGGTACAGTTCCACATGCGCC  
SG13S115

AGGGGGCAAAACATTCAAATAACTCAGGAGATAACACAACCTATTT  
GTTTTTAAGTGTGAGTTTTTAGGCAATCACAAAGATCCAGATGTATGTCCA  
AGCCTCTCTTTGCAATTCTAATTAACCTCAATGTTGCAACCATAGACCTAC  
CTTACAGAGTTCAAAAAAATATGCAAAAACCTGCCTTTCTTCTTCCTCAT  
[A/T]CCCCAAAATGCCATTCTGAACATTTCTGTAGTTAAAAAAGATTT  
CCATGGTGTACCAGGCACTGTACACAGTCTGTGTCCCAAGACAAGGAGG  
TACAGTTCCACATGCGCCCATGACTGGGTTGGGCTCTGCACTCTCTCTATA  
CTTTGAGAGCCTGATTTTCTGTGATTGGGCAGAGCTGGCCACCTGGTG  
SG13S116

TCTGCACTCTCTCTATACTTTGAGAGCCTGATTTTCTGTGATTGGGC  
AGAGCTGGCCACCTGGTGCAATGTCTCCTCTGCCTTTCAAACATGTTTT  
AGTCATCAAGATCTTCAAATTTGTAACCCTTTCCAGCTTGATCCAGCAGAA  
TGCAGATTTGGAAAAACAGAACGAGTTTAAAAATACATGATTCTAAGAAA[  
C/T]CTGGACCAGAACTATCAAACTTGGTTTCCCAGAGAATATAGCAAAT  
GGGCTCATTTGGCCAATACTATGACATTGGCTTTTGAGAAAAGAAAGGCTT  
TATTGCAAGGCTGGCCAGCAAGGAGACAGGAGTTGGGCTCAAATCTGTCT  
CCCCAGTTTGGGGCTTAGGGCAAGTTTAAATTACACAGACGCATTTCTTA  
SG13S117

AACCTTTCCAGCTTGATCCAGCAGAATGCAGATTTGGAAAAACAG  
AACGAGTTTAAATAACATGATTCTAAGAAACCTGGACCAGAACTATCAAA  
ACTTGGTTTCCCAGAGAATATAGCAAATGGGCTCATTTGGCCAATACTATG  
ACATTGGCTTTTGAGAAAAGAAAGGCTTTATTGCAAGGCTGGCCAGCAAG  
GA[A/G]ACAGGAGTTGGGCTCAAATCTGTCTCCCCAGTTTGGGGCTTAGGG  
CAAGTTTAAATTACACAGACGCATTTCTTATGAGTAGCAGGCAGAGAGCC  
TCCAACTTCTTCTGCCTAGGTACCAGCAGCTTAGACATGATGCAAACCTGG  
GAAGCACATACTGTATTTGGAGAAAGTGATTGGGAAGAAATGTGAGCTGA  
G

SG13S118

TACATGATTCTAAGAAACCTGGACCAGAACTATCAAACTTGGTTT  
CCCAGAGAATATAGCAAATGGGCTCATTTGGCCAATACTATGACATTGGCT  
TTTGAGAAAAGAAAGGCTTTATTGCAAGGCTGGCCAGCAAGGAGACAGG  
AGTTGGGCTCAAATCTGTCTCCCCAGTTTGGGGCTTAGGGCAAGTTTAAAT  
TA[C/T]ACAGACGCATTTCTTATGAGTAGCAGGCAGAGAGCCTCCAACTTC  
TCTGCCTAGGTACCAGCAGCTTAGACATGATGCAAACCTGGGAAGCACA  
TACTGTATTTGGAGAAAGTGATTGGGAAGAAATGTGAGCTGAGGGGAGG  
GGCTCAGTGCCCTGAGCTACACTTAGTGATGGCAGAGGAAGGATGTCCT  
CCC

SG13S119

TGGGGCTTAGGGCAAGTTTAAATTACACAGACGCATTTCTTATGAG  
TAGCAGGCAGAGAGCCTCCAACTTCTTCTGCCTAGGTACCAGCAGCTTAG  
ACATGATGCAAACCTGGGAAGCACATACTGTATTTGGAGAAAGTGATTGG  
GAAGAAATGTGAGCTGAGGGGAGGGGCTCAGTGCCCCTGAGCTACACTTA  
GT[A/G]ATGGCAGAGGAAGGATGTCCTCCCGCAGGAGGCTGTTCCACATCT  
GCTCTGGTTGTAGGGGGAGCTGGCAGGCATTAGCAGCGGCCTCTTTCCCC  
CAAGAGAGGCAGCCTCCTCCAAGTTTGGCGACATTATGGCCCTGCAATC

FIG. 8.17

ATAAGGGTTTGTGAGCATAGTGCTAAGGAGGGAAATGGAGCTGCTGTTAC  
TA

SG13S120

CCTCCTGAGTAGCTAGGACTACAAGCATGTGCCACCACGCCAGCT  
AATTTTTGTATTTTAGTAAGGACAGGGTTTCACCATGTTGGCCAGGTTGG  
CCTCCAACCTCCTGACCTCAAGTCATCCTCCTGCCTCGACCTCCCAAAGTGC  
TGGGATTACAGGCATGAAACCAGCCTAGAAATACATACTATTATTTATTC[  
C/T]TGTTTTACAGATAAGCAAAGTGAGTCATGGAGAATTTGGTTGAAAGT  
CCCAAGGTCAGGAGTCGTGAAGCTGGGATTAAACCTAATCATCTGACTT  
TAGAGAGTAGACACTTGCTCCATGCATATTGCCTCCAATTCATTCAA  
GCACTCCCTGCTCAAGAAGTTCCTTCTTATGTTGAGCTGAAATCTGCAG

SG13S121

TCATCTGACTTTAGAGAGTAGACACTTGCTCCATGCATATTGCCTCC  
AATTCATTCAATCAAGCACTCCCTGCTCAAGAAGTTCCTTCTTATGTTGAG  
CTGAAATCTGCAGCCCTATGCGTTTTACCCAGCAGTCCTGGTGCTGTTCCC  
TAAATCACTTAGACTGTGCCTGCTCTTTCTGTGTTACAGTGTGAGCT[A/  
G]TAATATCCCCCTCTTCGGCCTAACGTTTCTGAAGTCCCTTGCCACTGGGT  
CTCCTCTCCTCTTCCTGTGTTCTTTCTAAGAACACCTATGCAGATAGGTGTC  
TTCTGTACAGGGAAGCTGTTCCCTGAGATCCGGGCATCGACTCTGTTAGAAT  
AATCTACGTATGAGTTATTTTTTTGAGAACTATGTGTCATTGCT

SG13S122

ATGTTGAGCTGAAATCTGCAGCCCTATGCGTTTTACCCAGCAGTCC  
TGGTGCTGTTCCCTAAAATCACTTAGACTGTGCCTGCTCTTTCTGTGTTTAC  
AGTGTGAGCTGTAATATCCCCCTCTTCGGCCTAACGTTTCTGAAGTCCCTT  
GCCACTGGGTCTCCTCTCCTCTTCCTGTGTTCTTTCTAAGAACACCTAT[A/G  
]CAGATAGGTGTCTTCTGTACAGGGAAGCTGTTCCCTGAGATCCGGGCATCG  
ACTCTGTTAGAATAATCTACGTATGAGTTATTTTTTTGAGAACTATGTGTC  
ATTGCTGACTCATATTAACCTCTGTGGTTAACTAAAATCTCAAGATCTCTTT  
ATGTTTGTTGAGAACTTATTTAACTTCTCTGGCCCTCCGTTTCC

SG13S123

GTCCTGGTGCTGTTCCCTAAAATCACTTAGACTGTGCCTGCTCTTTC  
TGTGTTTACAGTGTGAGCTGTAATATCCCCCTCTTCGGCCTAACGTTTCTG  
AAGTCCCTTGCCACTGGGTCTCCTCTCCTCTTCCTGTGTTCTTTCTAAGAAC  
ACCTATGCAGATAGGTGTCTTCTGTACAGGGAAGCTGTTCCCTGAGATC[C/T  
]GGGCATCGACTCTGTTAGAATAATCTACGTATGAGTTATTTTTTTGAGAA  
CTATGTGTCATTGCTGACTCATATTAACCTCTGTGGTTAACTAAAATCTCAA  
GATCTCTTTATGTTTGTGAGAACTTATTTAACTTCTCTGGCCCTCCGTTT  
CCTTCACTGAGCAGTGGAGTGATTGATAACCTCCACCTGTGGTT

SG13S43

CACCTATGCAGATAGGTGTCTTCTGTACAGGGAAGCTGTTCCCTGAG  
ATCCGGGCATCGACTCTGTTAGAATAATCTACGTATGAGTTATTTTTTTGA  
GAACTATGTGTCATTGCTGACTCATATTAACCTCTGTGGTTAACTAAAATCT  
CAAGATCTCTTTATGTTTGTGAGAACTTATTTAACTTCTCTGGCCCTC[A/  
C]GTTTCCTTCACTGAGCAGTGGAGTGATTGATAACCTCCACCTGTGGTTG  
CTGAAGGTCTTGACAAGATGATATAGTTAAAGTAGCTAGCAGTGCCAC  
GTACGGCGGATGCCTCACACGTTTGCAGCCATCTCTCTATCTGTGTCTT  
TGTCTCTCTCACACTGGTTTTGGCTTACTGTTAGCAGCTAGCCGA

SG13S399

TCTGTGGTTAACTAAAATCTCAAGATCTCTTTATGTTTGTGAGAAA  
CTTATTTAACTTCTCTGGCCCTCCGTTTCCTTCACTGAGCAGTGGAGTGATT

FIG. 8.18



GATAACCTCCACCTGTGGTTGCTGAAGGTCTTGCACAAGATGATATAGTT  
AAAGTAGCTAGCAGTGCCACGTACGGCGGATGCCTCACAACGGTTTGC[  
A/C]GCCATCTCTCTATCTGTGTCTTTGTCTCTCTCTCACACTGGTTTTGGCT  
TACTGTTAGCAGCTAGCCGAGATAAGTGTGTTTATGGTCTTTGCATGTATT  
GTTTCTGTAGCATACTGGAGGATTACAAGAGGTTGGGGAGTGAGGGGGCG  
GTGAGGAGTAGACAAAGGCAGCCAACTCTTCCAAGTTTAGCTTAGAA  
SG13S124

TTGATAACCTCCACCTGTGGTTGCTGAAGGTCTTGCACAAGATGAT  
ATAGTTAAAGTAGCTAGCAGTGCCACGTACGGCGGATGCCTCACAACGG  
TTTGCAGCCATCTCTCTATCTGTGTCTTTGTCTCTCTCTCACACTGGTTTTG  
GCTTACTGTTAGCAGCTAGCCGAGATAAGTGTGTTTATGGTCTTTGCATG[  
C/T]ATTGTTTCTGTAGCATACTGGAGGATTACAAGAGGTTGGGGAGTGAG  
GGGGCGGTGAGGAGTAGACAAAGGCAGCCAACTCTTCCAAGTTTAGCTTA  
GAAGGAAGGAGCGGTAAACCCTAGTTGAATGTTGGACTGAAGCAGGTTTG  
TTTTTGTTTTGTTTAAAGGATAGGGAAGATCTGTGCGTGTTTCCAGGATA  
SG13S125

ACTTGAAGTCAGTGGCATGGACAGGGTCAAGATCACAGTTAGAGG  
ATGCAGCCTTAGAGAAAAGGAAGGGGCTCGGTTCTCTGAGCAAGGAGGG  
AAAGAAGAGAGGCAGATGCAGAGAAGTACGGCACATCGTGCTGCTGGTT  
GTAGAAATAACCTCTGACTTTTAATAAAGTCATCCCTCGGTATCCCTGGGG  
GATT[A/G]GTTCTATGACCTCCCTCGGATGCCAAAATTTCGTGGATGCTCAA  
GTCCCTGATATAAAATGGCATAGTATTTGCATTTAACCTACACACATCCTC  
CATATCCTTTTTTTTTTTTTTTTTTTTTTTTTTTTTTTTTTTGTGAGATGGAGT  
CTTGCTCTGTGCGCCTGGCTGGAGTACAGTGGCTCGATCTTGGCTCACT  
SG13S400

AATACCTGATAGAATGTAAATGCTATGTAAACAGTTGTTATACTGT  
ATTGTTAAAAGACAGTAACAAGAAAAAAATCTGTACATGTTCAAGTCCAG  
ACAAATGGTTTTCTGTTTTTTTTTTTTTTTTTTTAATATTTTTGGTCAAGTGGT  
GGTTGACTCCAGGAATGCAGAACCCGCAGATATAGAAGGTTGATTATGC[  
A/G]JTCAGAGGCAGGGAATACCATCTTGGGTTCCAGAAAGAAAATGATCA  
GCATTTTCTGTCACTCTGGTAAAAACAGATCTTTTGAATGGACAGGTGT  
ATTAAACCCTGTGGAGCTGGCTGGGCTGGCGGCTCACGCCTGTAATCCC  
AGCACTTTGGGAGGCTGAGGCAGGTGGATCACGAGGTCAGGAGTTCGAG  
SG13S126

TGCCCCGCAGAGTTTGAAGTCCCGGCTGCACCTCTCCCCAGCAGCA  
GGTTGACTCTGGAAAGTTGCAGCGTTCTTACCTACAGAGTGGGAACAGTA  
CTACCCATTGCACAGAGTGGGTGCAAAGCTCTGTGACGGAATACATGGCA  
AGTGCCCAACCATTTGCCTGGGATGAGGTGGGCCCTTCCTTTACGTAAGA  
GA[A/G]CCCTACAGATACACTCAAAGTGGGCACATTCCTACAGAAGGAGT  
GTTATTTGTGTAGAAAAGAAAAACATGAAAGGCTTTTATTCCTATACACA  
ATAAAGCACCCCTTTAATGTCTTTTTGAGGAGGATAATATGAAATTGATGA  
AAAGGAACCCTGTGGTTGGATCCCTGACAATCACATGTATCCCTTTTTTCA  
C  
SG13S127

TACAGATACACTCAAAGTGGGCACATTCCTACAGAAGGAGTGTTAT  
TTGTGTAGAAAAGAAAAACATGAAAGGCTTTTATTCCTATACACAATAAA  
GCACCCCTTTAATGTCTTTTTGAGGAGGATAATATGAAATTGATGAAAAG  
GAACCCTGTGGTTGGATCCCTGACAATCACATGTATCCCTTTTTTCACTCT  
T[A/G]AAAAAGGAGTAAAGGAATAAAATAGAANNNNNNNNNNNNNNNNNN  
NN

FIG. 8.19



SG13S193

GCTCCTGAACATGCCCCACAATGAACCAGATGCAAACCTTTTCCCTT  
GGCAGGATTCTTTGCCCATAAAGTGAGACGAAAGCAGGACCCAGAAT  
GGGAGGAGCTTCCAGAGGACCGGAACACTTGCCTTTGAGCGGGTCTACAC  
TGCCAAGTGAGTCCTAACCCTGATGTTGCTAATAAGTGGGGGCATGGGCA  
GGG[A/G]GGCCTCCTTCTAGGAGTGATGACCACCCTTAATACCACATGTCT  
GTCTGAGCCAAGTTTCTGAGCGCCAGGGAGGTGAGGAAGGTTGGACTTCA  
CCAGAGAGGCTTTGTGGACACCCTTTATCATCTTAGTGAGTGCTAGTGTCA  
AAACAAAGGGAGTGGGGATATGGGGCACATTGGTGGAGGGAGGTGTGAT  
CTC

SG13S88

TTGCCCATAAAGTGAGACGAAAGCAGGACCCAGAATGGGAGGA  
GCTTCCAGAGGACCGGAACACTTGCCTTTGAGCGGGTCTACACTGCCAAG  
TGAGTCCTAACCCTGATGTTGCTAATAAGTGGGGGCATGGGCAGGGGGGC  
CTCCTTCTAGGAGTGATGACCACCCTTAATACCACATGTCTGTCTGAGCCA  
AG[C/T]TTCTGAGCGCCAGGGAGGTGAGGAAGGTTGGACTTCACCAGAGA  
GGCTTTGTGGACACCCTTTATCATCTTAGTGAGTGCTAGTGTCAAAACAAA  
GGGAGTGGGGATATGGGGCACATTGGTGGAGGGAGGTGTGATCTCTGCAG  
CTTCAGAAAGATCTGAAAGAGTCATTTGGTTAGAGAAGTTGACCTATTTCC  
T

SG13S131

AAACAAAGGGAGTGGGGATATGGGGCACATTGGTGGAGGGAGGTG  
TGATCTCTGCAGCTTCAGAAAGATCTGAAAGAGTCATTTGGTTAGAGAAG  
TTGACCTATTTCTGTGGGGTTAGACCAGGGTTGCTACTGTGAACACCAGC  
CATGACTCACCAGTCACCTTCAGAAGCCACAGGCAGGACATGCTGACGAC  
AG[C/T]CTTCAACTCACCCACCCCTTGCTCCCCTGCGGGTGGAAGTCTGGA  
GGTGACACCACTGCATTTTCTAACACGGGGGCTCCTTGAGCAACTAGAAC  
AAGAACAGAAAGAATGGGGACATTAGCAGGTGCTTTCCCCCTCTCTCATT  
CTTTTCTTTGAATAAAAAGGTTGTTTGAACACCTGAGCGGCTCCTAAAG  
A

SG13S132

CTCCTCTCTTCTTTATGCAGAGTGATTTCAAGGCTCAGCCAGTGGC  
AGGCATGCTGGGGACTATGGACTACGGACTAGGGGCCTGTACAGAGGA  
AGGCCTCATGCTAGAGAGCTAAGGGAGGAGCTGGCCTTCAGTTCCATCCC  
AGGAGCAACTTTGATGTTCCCAGAGATCCTTCCAAAGGGGGAGTCATGGT  
CA[A/C]CCAAGAAAAATGTATTGAGAATGCCAAGAATGGTGCAAACCTCAG  
GACAAAGATTACACTGCAGGGTTGGAGTCCCTGGGCTTGCTGCTGGCAC  
CATGGGAGGGAGGGTCCCCTTCAGGGGTACCGTTGGTTTCCTGTGAATTA  
AACTGGCTTCAAGGGATCTCGACTGAACAGGCCTATATCACACTCACTGA  
TAT

SG13S133

TCTCCTCATCTAGGTATTTTAAATTGTTTCAGTGAGGTGTAGGCATG  
AGGGGATTGGAGGGGGCATCTCCTCCATTGCAGTTTTTCATTGGCTGCTTT  
GCTCCCTCAGCTCCGAAATCGCTGGGCCACTCTCGAACGCATTAGTACGG  
TAGTCACAGGTTGATTGCCTGGCCCCCTTGCCCTCTGTGGGCATTTTCCCT[C  
/T]TCAGACAGCCCCTGAGTACTCACAGTGCTGCTACAGTGGGCCACCTAG  
ATCTCCCTCTTTCTCCATGCTCCCACGTGCTCTGGGCTCCACTCCCTTCTCC  
CAAGCACTTCTGTCCAGGGCTATTCCAGCAGTCTGACCTCAAGGAAATCC  
TTTGCTAAACTGATTATAGAGAGGTTTCTATTTTAAACATTTAGGTCT

FIG. 8.21

SG13S38

ATCTAGGTATTTTAAATTGTTTCAGTGAGGTGTAGGCATGAGGGGA  
TTGGAGGGGGCATCTCCTCCATTGCAGTTTTTCATTGGCTGCTTTGCTCCCT  
CAGCTCCGAAATCGCTGGGCCACTCTCGAACGCATTAGTACGGTAGTCAC  
AGGTTGATTGCCTGGCCCCTTGCCCTCTGTGGGCATTTTCCCTTTCAGAC[A  
/T]GCCCCCTGAGTACTCACAGTGCTGCTACAGTGGGCCACCTAGATCTCCCT  
CTTTCTCCATGCTCCCACGTGCTCTGGGCTCCACTCCCTTCTCCCAAGCACT  
TCTGTCCAGGGCTATTCCAGCAGTCTGACCTCAAGGAAATCCTTTGCTAAA  
CTGATTATAGAGAGGTTTCTATTTTAAACATTTAGGTCTTCCATGT

SG13S134

AGGTGTAGGCATGAGGGGATTGGAGGGGGGCATCTCCTCCATTGCA  
GTTTTTCATTGGCTGCTTTGCTCCCTCAGCTCCGAAATCGCTGGGCCACTC  
TCGAACGCATTAGTACGGTAGTCACAGGTTGATTGCCTGGCCCCTTGCCCT  
CTGTGGGCATTTTCCCTTTCAGACAGCCCCTGAGTACTCACAGTGCTGCTA  
[C/T]AGTGGGCCACCTAGATCTCCCTCTTCTCCATGCTCCCACGTGCTCTG  
GGCTCCACTCCCTTCTCCCAAGCACTTCTGTCCAGGGCTATTCCAGCAGTC  
TGACCTCAAGGAAATCCTTTGCTAAACTGATTATAGAGAGGTTTCTATTTT  
AACATTTAGGTCTTCCATGTATTAATTCTCAGAATCAATTTAAGATG

SG13S135

CCTTTCAGACAGCCCCTGAGTACTCACAGTGCTGCTACAGTGGGCC  
ACCTAGATCTCCCTCTTTCTCCATGCTCCCACGTGCTCTGGGCTCCACTCCC  
TTCTCCCAAGCACTTCTGTCCAGGGCTATTCCAGCAGTCTGACCTCAAGGA  
AATCCTTTGCTAAACTGATTATAGAGAGGTTTCTATTTTAAACATTTAGG[C/  
T]CTTCCATGTATTAATTCTCAGAATCAATTTAAGATGTTTAAAGGTGTGAT  
TTAAGACATTTTAAACCATTGAGGAGAGTACAGAAATTATGTCACTT  
GCTGTGAGCCTCTTTGCACCATCTGCAGAGAAAGATACTAGAGTCCCGCC  
TTGGACACATCCACATGCAAGAGGTGCAAAGAAGGTGTCTTTGATGA

SG13S136

TTCTCAGAATCAATTTAAGATGTTTAAAGGTGTGATTTAAGACATTT  
TAAACCATTTGGAGGAGAGTACAGAAATTATGTCACTTGCTGTGAGCCT  
CTTTGCACCATCTGCAGAGAAAGATACTAGAGTCCCGCCTTGACACATC  
CACATGCAAGAGGTGCAAAGAAGGTGTCTTTGATGAGGCAAGGTCAAAA  
CT[C/T]CTCCCCAGACGAAATCCAAAGAAGCATTCTACTATGCTATATC  
AGTTTGGAAGAAAAACTTCTGCCAGGTGACTGCATTCTCACTGGTCACA  
TTGTGTTTCTATGGACTCCTCAGCTCAACCAATTTGGAGAAGTTATGGTGC  
AATTTACCATATCTGGTTAGAAGTTAAGTTTCCAATTTGCTGGCAATGAA  
SG13S137

AAGAAGGTGTCTTTGATGAGGCAAGGTCAAACTTCTCCCCAGACG  
AAATCCAAAGAAAGCATTCCTACTATGCTATATCAGTTTGGAAAGAAAAA  
CTTCTGCCAGGTGACTGCATTCTCACTGGTCACATTGTGTTTCTATGGACT  
CCTCAGCTCAACCAATTTGGAGAAGTTATGGTGCAATTTACCATATCTGG  
[C/T]TAGAAGTTAAGTTTCCAATTTGCTGGCAATGAAGAAGAAATGGAGCA  
GGCCAGGCTGTGTAGTTTCTGCCACGTGCCCCCGGGAGTGAACAGCTCTG  
TTTGTAAGAAGCCATGGTGCTTAGACCTGGGCTCGCTAGTTGCCAGCCTCC  
AAATTGCAGAAGTGCCCTTTGGTTGGTGGCTATGCTGTGTCACTTGGGA  
SG13S86

GCAACATATCTGTGTGCCTGTCTGGGTTGTAAAAAGGGTCAAAGAT  
CAATGCAGCAGGCAGCTACATGCTGGCAAAAGCCAGAGGCAGCTGGTCT  
GTTTGCCTGTGCCAGGAAACCACTGGGAATGGGGTTGTGTGTTATTCTAGG  
AGAAAGTCGTCCAGCAGCAGCTTCTCCAGGGGCATCCAAGAGCACTGAA

FIG. 8.22

AA[A/G]GGTTGCAAGATGACCCATGAGGCTGCAGGAAGAAAAGAACATGC  
ATTTAATCTTGCTATCTGAAAAGTAAGACATGAAGCTTTCCTCATTTTAA  
TATACACATGGACAGTAGTATGTGTATATAGTTTATATGCAAATATACTTG  
TTATAAGGTTGCATGCTCAAAATTTTTGGTTCATGGGGTGTGGGATCATAA  
SG13S87

CAGCTACATGCTGGCAAAGCCAGAGGCAGCTGGTCTGTTTGCCTG  
TGCCAGGAAACCACTGGGAATGGGGTTGTGTGTTATTCTAGGAGAAAGTC  
GTCCAGCAGCAGCTTCTCCAGGGGCATCCAAGAGCACTGAAAAGGGTTG  
CAAGATGACCCATGAGGCTGCAGGAAGAAAAGAACATGCATTTAATCTTG  
CT[A/G]TCTGAAAAGTAAGACATGAAGCTTTCCTCATTTTTAATATACACA  
TGGACAGTAGTATGTGTATATAGTTTATATGCAAATATACTTGTTATAAGG  
TTGCATGCTCAAAATTTTTGGTTCATGGGGTGTGGGATCATAAATGTTTAG  
GGACCATGGCTATCAAGGAAAAACAGCATGAAGGATAAATGATACTGGT  
G

SG13S138

CTATCTGAAAAGTAAGACATGAAGCTTTCCTCATTTTTAATATACA  
CATGGACAGTAGTATGTGTATATAGTTTATATGCAAATATACTTGTTATAA  
GGTTGCATGCTCAAAATTTTTGGTTCATGGGGTGTGGGATCATAAATGTTT  
AGGGACCATGGCTATCAAGGAAAAACAGCATGAAGGATAAATGATACTG  
G[C/T]GGATTAAAAAGACAGATGCATGTATTTTAGCATAAAACACAACCTG  
CTGACTGATACAGATAGCTCAAGATTCTGGGGCAGCTGCTGAACAGATAC  
ACTAGCCAGTGTGGCTCATCGGCTCAGACTTGGCCTTAATTAATGGGCTGT  
CCCTCCACCCATCTCCCATGAGGGCAGAGCTGAGCCAGGGTTTGAGAGCT  
SG13S139

AGTTTATATGCAAATATACTTGTTATAAGGTTGCATGCTCAAAATTT  
TTGGTTCATGGGGTGTGGGATCATAAATGTTTAGGGACCATGGCTATCAA  
GGAAAAACAGCATGAAGGATAAATGATACTGGTGGATTAAAAAGACAGA  
TGCATGTATTTTAGCATAAAACACAACCTGCTGACTGATACAGATAGCTC  
AA[C/G]ATTCTGGGGCAGCTGCTGAACAGATACACTAGCCAGTGTGGCTCA  
TCGGCTCAGACTTGGCCTTAATTAATGGGCTGTCCCTCCACCCATCTCCCA  
TGAGGGCAGAGCTGAGCCAGGGTTTGAGAGCTAAAAGGAATTGGACCTG  
GACTCTGTTCACGTGTATATTTTAATTCTAATTAATTCAATTCTTTTGAAAGA  
SG13S140

GTATTTTATGATATAAAACACAACCTGCTGACTGATACAGATAGCTCA  
AGATTCTGGGGCAGCTGCTGAACAGATACACTAGCCAGTGTGGCTCATCG  
GCTCAGACTTGGCCTTAATTAATGGGCTGTCCCTCCACCCATCTCCCATGA  
GGGCAGAGCTGAGCCAGGGTTTGAGAGCTAAAAGGAATTGGACCTGGAC  
TC[A/G/T]GTTACGTGTATATTTTAATTCTAATTAATTCAATTCTTTGAAAG  
ACAGAGTCACACTCTGTTGCCTAGCCTGGAGTGCAGTGGCACGATCTTGG  
CTCACTGCAACCTCGGCCTCCAGGTTCAAGTTATTCTCCTGCTTCAGCCT  
CCTGAGTAGCTGGGATTATAGGCACATGCCCCCATGCCTGACTAATTTT  
SG13S141

GCTAAAAGGAATTGGACCTGGACTCTGTTACGTGTATATTTTAAT  
TCTAATTAATTCATTCTTTTGAAAGACAGAGTCACACTCTGTTGCCTAGGC  
TGGAGTGCAGTGGCACGATCTTGGCTCACTGCAACCTCGGCCTCCAGGT  
TCAAGTTATTCTCCTGCTTCAGCCTCCTGAGTAGCTGGGATTATAGGCACA  
[C/T]GCCCCCATGCCTGACTAATTTTTGTATTTTAGTAGAGACGGGGTTTC  
ACCATGTCAGGCTGGTCTTGAACCTCCTGACCTCAGGTTATCCACCCGCCTT  
GGCCCCCTCAAAGTGTTGGAATTACAGGTGTGAGCCACCGTGCCTGGCCTG  
TTCACATGTATAAAACACAGTTTAATGTCCTATTCCCAGCCAATGAGC

FIG. 8.23

SG13S39

TCAGGTTATCCACCCGCCTTGGCCCCCTCAAAGTGTTGGAATTACAG  
GTGTGAGCCACCGTGCCTGGCCTGTTACATGTATAAAACACAGTTTAAT  
GTCCTATTCCCAGCCAATGAGCATGGCTAGAGCAGCCTTGGTCAAAGTTT  
GGTTTTTGGAGAAAAATCCTTGTTAGCTGACCTAAGATTCTCTTTGTGAG  
T[G/T]TAAGTAAGCACAGGTTGCAGAGAGGAGAAGGGTCTCTGGAGAGGT  
GTAATTTTCTAAATGGATTACAAGTTCATGGACTTTTAACAGGTGTTACAG  
GGGATAACAAGTTCTTTATAGACAGACTTTTGAGGACGTTTAAGGGTATTC  
TGATTCTTGGTTTTCTAAGAGGGGAATGTATTATTTAACTACAGACACCC

SG13S142

AAAATCCAGAATAATAATAATTTGTCAATAGGAAAGACATTTCCAC  
TGGGGGTAAAGAAGGAAGACATTGGAACAATGATAGCCACCACTTATTGA  
ATGCTTACTGTGAGCCAGGTGGCACTTCACCTTGTTTCATTCTCACAAACAG  
TCTAGGGAAGTAATTACTAATGTCTCCATCCACCTCTTGTAGATGAGCAAA  
[C/T]TGAGGCTCATTGAGGCTAGGAAATGCACCCACACTCACATAGCCCAT  
AAGAGGCAGCCATGGCATTGGGCCCAGACCATGTGAACTTCAAAGACTAC  
ACGAGCAGCCACTGGGCAGCTGTCATGGCTAAAGCCACTTGAATTCAGCC  
CAGCAGCAACCCCTCTCCAGGAGGGGCACATAAGCTTGCAGCTTTGGGT

SG13S143

ATAATAATAATTTGTCAATAGGAAAGACATTTCCACTGGGGGTAA  
GAAGGAAGACATTGGAACAATGATAGCCACCACTTATTGAATGCTTACTG  
TGAGCCAGGTGGCACTTCACCTTGTTTCATTCTCACAAACAGTCTAGGGAAG  
TAATTACTAATGTCTCCATCCACCTCTTGTAGATGAGCAAACCTGAGGCTCA  
[C/T]TGAGGCTAGGAAATGCACCCACACTCACATAGCCCATAGAGGCAG  
CCATGGCATTGGGCCCAGACCATGTGAACTTCAAAGACTACACGAGCAGC  
CACTGGGCAGCTGTCATGGCTAAAGCCACTTGAATTCAGCCCAGCAGCAA  
CCCCCTCTCCAGGAGGGGCACATAAGCTTGCAGCTTTGGGTAGAAGCTGC

A

SG13S144

GCACTTGAAGTCCTGGATGGCGAGAGGGACTGGCTTGAGCCAGAG  
CCAGGAACAAGGCTCTGAGAATATTCTGGAAATCCACAGGAGGAACCCAT  
TTTCTTACAGCTGGGAGAATTTCACTTCAACTCCAGGCTGACCATGTTTTAT  
TAGGAACGAAGGTGACTTGAACATAAGTCAGGAATGGTTGAATACGGAC  
CC[A/G]ATGTCAAATCACTAGGCAGTTCACATTTCTAATGAGCAAATCCCT  
TAGACAATTAAGAATTTTTTTCCTTTTGCATAACCCAGACAAAATCGCTAC  
TAAAAACAAACCAAAGACCCGAAACATGAGAAAGAGAAGGAAGCAGG  
GGAAATCTTTGGTACTAATAAGTTTTTAAACAATAAGAGCACCAGATATTT  
TA

SG13S145

ATGAGCAAATCCCTTAGACAATTAAGAATTTTTTTCCTTTTGCATAA  
CCCAGACAAAATCGCTACTTAAAAACAAACCAAAGACCCGAAACATGAG  
AAAGAGAAGGAAGCAGGGGAAATCTTTGGTACTAATAAGTTTTTAAACAA  
TAAGAGCACCAGATATTTACCCCATCAGACACAGAATGTTATTCGAATA  
AC[C/G]AAAAAAGGAATTTTTTCTCTAAGTTTCTTGAAGTGGAAAATGAAT  
CATATTTTCTCAGTCCTGAGGCTGCAATTTTGTGCCTCTAGTAACATATAA  
GAATAGATGTGATGCCAGTGCCAGTAGCTGCTGCAATTGTTACTTGGGG  
ACCTGTTTATTCTAAGCACTTCACCCAGTGATAAATTTGTAGGGGCCT

SG13S146

CCGTGTCCATTAGATCAGTGGAATTCTGGGATTCAGAGCACTTTG  
CAAGGTCAGCAGGGGTCTGCTCTTTCTGTCCTGTTCTGGTTTTTGGTTGTG

FIG. 8.24

CCTGGATTCCAGGGTAGGTTTCTCATCTGTTACCTTCATAGACTTCTCCAG  
AAAAGGATCTTTTGACCATCAGAGGACCACGAAGATTCCATTGGTGAGG[  
C/T]GCAGATAACCTGATCTCTCTGGGTTCTCTGCAGGGCACAGATGAAGG  
GCTGGCCATTCCCAAGTTCTCAGTGGTACCCTGAGGCATGAGACCCTAA  
TGGTTTGCATGAGCAGTTTGAAAATTGCATCTTTGTTTTACCTATATAATC  
ACATGAAACCCGTGGTTCTCAAACGTCAGCAGGCATCAGCATCACATG  
SG13S26

TCAGTGGTACCCTGAGGCATGAGACCCTAATGGTTTGCATGAGCA  
GTTTGAAAATTGCATCTTTGTTTTTACCTATATAATCACATGAAACCCGTG  
GTTCTCAAACGTCAGCAGGCATCAGCATCACATGGAGGGCTTGTTAAAC  
AGATTTCTGGGCCCCAACACAGAGTTTTAAATTCTGAAGGCCTGAGGTGG  
G[C/T]GTGAACATTTGCATTTCTAACATGTTCTCGATGCTGCTGCCGCCTCT  
GGTCCCGAGAGCATGCCTGGGAGAACTGCCACCTTCGACCATGGACTGTGA  
GAATTCACATGGACCTCAGAATTATAATCAGTCTCTCAGTTTTACAGATAA  
GGAAACTAAATCCAGAGAGATTGTTTTGCCAATGGTGAACAGCTGGTTA  
SG13S27

ATGGTTTGCATGAGCAGTTTGAAAATTGCATCTTTGTTTTTACCTAT  
ATAATCACATGAAACCCGTGGTTCTCAAACGTCAGCAGGCATCAGCATCA  
CATGGAGGGCTTGTTAAACAGATTTCTGGGCCCCAACACAGAGTTTTAA  
ATTCTGAAGGCCTGAGGTGGGTGTGAACATTTGCATTTCTAACATGTTCTC  
[A/G]ATGCTGCTGCCGCCTCTGGTCCCGAGAGCATGCCTGGGAGAACTGCCA  
CCTTCGACCATGGACTGTGAGAATTCACATGGACCTCAGAATTATAATCA  
GTCTCTCAGTTTTACAGATAAGGAACTAAATCCAGAGAGATTGTTTTGCC  
AATGGTGAACAGCTGGTTAAAGTCAGGATGGAGACTTTAATCCTAGTCA  
SG13S147

GAGCAGTTTGAAAATTGCATCTTTGTTTTTACCTATATAATCACATG  
AAACCCGTGGTTCTCAAACGTCAGCAGGCATCAGCATCACATGGAGGGCT  
TGTTAAACAGATTTCTGGGCCCCAACACAGAGTTTTAAATTCTGAAGGC  
CTGAGGTGGGTGTGAACATTTGCATTTCTAACATGTTCTCGATGCTGCTGC[  
C/T]GCCTCTGGTCCCGAGAGCATGCCTGGGAGAACTGCCACCTTCGACCAT  
GGACTGTGAGAATTCACATGGACCTCAGAATTATAATCAGTCTCTCAGTTT  
TACAGATAAGGAACTAAATCCAGAGAGATTGTTTTGCCAATGGTGAACA  
GCTGGTTAAAGTCAGGATGGAGACTTTAATCCTAGTCAAGTGACCTTTC  
SG13S28

AGTTTGAAAATTGCATCTTTGTTTTTACCTATATAATCACATGAAAC  
CCGTGGTTCTCAAACGTCAGCAGGCATCAGCATCACATGGAGGGCTTGTT  
AAACAGATTTCTGGGCCCCAACACAGAGTTTTAAATTCTGAAGGCCTGA  
GGTGGGTGTGAACATTTGCATTTCTAACATGTTCTCGATGCTGCTGCCGCC  
[G/T]CTGGTCCCGAGAGCATGCCTGGGAGAACTGCCACCTTCGACCATGGAC  
TGTGAGAATTCACATGGACCTCAGAATTATAATCAGTCTCTCAGTTTTACA  
GATAAGGAACTAAATCCAGAGAGATTGTTTTGCCAATGGTGAACAGCTG  
GTAAAGTCAGGATGGAGACTTTAATCCTAGTCAAGTGACCTTTCCTCT  
SG13S148

CATCTTTGTTTTTACCTATATAATCACATGAAACCCGTGGTTCTCAA  
ACGTCAGCAGGCATCAGCATCACATGGAGGGCTTGTTAAACAGATTTCT  
GGGCCCCAACACAGAGTTTTAAATTCTGAAGGCCTGAGGTGGGTGTGAAC  
ATTTGCATTTCTAACATGTTCTCGATGCTGCTGCCGCCTCTGGTCCCGAGA[  
G/T]CATGCCTGGGAGAACTGCCACCTTCGACCATGGACTGTGAGAATTCAC  
ATGGACCTCAGAATTATAATCAGTCTCTCAGTTTTACAGATAAGGAACT

FIG. 8.25

AAATCCAGAGAGATTGTTTTGCCAATGGTGAACAGCTGGTTAAAGTCAGG  
ATGGAGACTTTAATCCTAGTCAAGTGACCTTTCCTCTGTATTTATTTCCC  
SG13S98

ATTTCTGACATCCTGAACCATAGTAAAAGGGTGTTTTTTGTTTTTTT  
GAGACAGAGTCTTGCTCTGTTGCCTGGGCTGGAGTGCAGTGGTGTGATCTT  
GGCTCGCTGCAACCTCCGCCTCCCAGGTTCAAGTGATTCTCCTGCCTCAGC  
CTCCTGAGTAGCTGGGATTACAGGTGCTTGCCACCACACCTGGCTATTT[G/  
T]TTGTGTTTTTAGTAGAGACAGGGTTTCACCATGTTGGCCAGGCTGGTCTT  
GAACTCCTGACCTTGTGATCTGCCTGCCTCAGCCTCCCAAATTGCTGGGAT  
TACAAGGCGTGTTGTTTTAAGCCACTCAGTTTGTGGCCACTTGTTACAGCA  
GCAAGAGGAACTCATACAGTTATCATGTGAACTCACAGGAATAT  
SG13S149

GATCTGCCTGCCTCAGCCTCCCAAATTGCTGGGATTACAAGGCGTG  
TTGTTTTAAGCCACTCAGTTTGTGGCCACTTGTTACAGCAGCAAGAGGAA  
ACTCATACAGTTATCATGTGAACTCACAGGAATATGGTGAGTTAAAAAGA  
GAGGAAGGGTGCAAAACATCCACGGTAGAGTGAGAACTCTCCAGGGAGT  
GAG[A/G]ACTGTGCCCAGCATACAGTGATCACCTCTTAGTAAGCTAAGTT  
TCTGAGCACCAGCTTTTTTGAGTTGACTTTGTTGTCTTTAACATTTGAAGAT  
CACCTTCTTTGCTCAGCCTGGCTTGACAGACCTGGGCTGATTTGTGGATCT  
GATAGAAAAGTTTCCTTAGTTGGGCTCTTCTCCCCGACCACCCCATGCC  
SG13S29

TGCCTCAGCCTCCCAAATTGCTGGGATTACAAGGCGTGTTGTTTTA  
AGCCACTCAGTTTGTGGCCACTTGTTACAGCAGCAAGAGGAACTCATAC  
AGTTATCATGTGAACTCACAGGAATATGGTGAGTTAAAAAGAGAGGAAG  
GGTGCAAAACATCCACGGTAGAGTGAGAACTCTCCAGGGAGTGAGGACT  
GTGC[A/C]CAGCATACAGTGATCACCTCTTAGTAAGCTAAGTTTCTGAGC  
ACCAGCTTTTTTGAGTTGACTTTGTGTCTTTAACATTTGAAGATCACCTT  
CTTTGCTCAGCCTGGCTTGACAGACCTGGGCTGATTTGTGGATCTGATAGAA  
AAGTTTCCTTAGTTGGGCTCTTCTCCCCGACCACCCCATGCCAGTGTTGGC  
SG13S89

GCTACTTTGCAGCCAAGGTAACCTCAGACTTCCCTTTGTTCAATTCTCC  
TTCTATAAAGTGCACTCTCAAGGAGGTTCAAAGGGCAGGCTTTTTGTTGAA  
AGGACTTTGCCTGACCTCTGGCTCCCCTCTGTGAAGCCCTGGAGAGGTGA  
GAGCCCTCGGGAGGCCGTGTTTCAGGCATGCTCTGCACCCGTGCAGAGCG  
C[A/G]TGTGATAATGCATTGCTAATGCTTGCTCCCTGGTGGCTGGCTGAGA  
GCTGCTGTGCTGACAAGGGTGGTTTAAGGCTAAATGTGACTCAGAATCCT  
TAAGCAGTGTTAGTTCAGATACAAGGGCATTATAAATGAGAGTGCCTGAG  
GGATCTATTTTGGGACCGCTGTCACTTGGCTCTTCTGCTAATAAGCTTCCA  
SG13S96

ACAGTTATCAGCAGCCCACAGGCTTGACTTGAGCAAGTTGGAAAG  
ACAAATCAACTTCCAGAGTTGATTTAACATTGAGTGGAAATCAGTCATAC  
TTTTGGTCCCCTTTCTGGGGCCACGCCTGGCACTGTGCCTGGTGGCAGATCG  
GCATGAACTGGCCAGCTTCTGTGGCCCTGGAGGGCACAGGCAGAAAGGCC  
AC[A/G]CTCAGTCCCATGATGAACTGTTTAAGACTTATTGTTGTCTCCCCGC  
TCTGTAAAGTAGATAGAGTGGATTTTATGTCCCTTATTACCTTTCAGGATA  
CTTTGACTCAGGGAGATAAAGTAACTTGGGTACAGCTACTCAGCTGGTGA  
AGAACACAGGCAGAAATGAGTGCCTGGGTCTTTTGACTIONAAAATTCTGGAT  
SG13S150

CTGTGCCTGGTGGCAGATCGGCATGAACTGGCCAGCTTCTGTGGCC  
CTGGAGGGCACAGGCAGAAAGGCCACACTCAGTCCCATGATGAACTGTTT

FIG. 8.26



AAGACTTATTGTTGTCTCCCCGCTCTGTAAAGTAGATAGAGTGGATTTTAT  
GTCCCTTATTACCTTTCAGGATACTTTGACTCAGGGAGATAAAGTAACTTG  
[C/G]GTACAGCTACTCAGCTGGTGAAGAACACAGGCAGAATGAGTGCCTG  
GGTCTTTTGACTTAAAATTCTGGATTTTTCACAAAGATCCTCTTACTTTATT  
CATTTACATAATAAAATATATATTGAAGAGCTACTCTGTGCCAAGCCCTGTG  
CCTAGATATACAGTGATAAATAAAGAGTAGCTTCTAGAGGTCACCTGG  
SG13S401

AAGTTCAGTGATAGAGAGCAGAGGTGAGGCGGCAGCAGAAACCAC  
TTAAGGGACACCACGTGGCACTCCTTCTGTGCTGAGAAGGCTGTCAGTAA  
GCTCACCATTTATTTCTATTTTCTCTCCTGAGTTAAATAGGAAACATGTCT  
CGCATTACTTGAAAAATCAAGTCAAACATGCTCTTACTAGGAGTTATGGT  
[C/T]CTTTTATGTCTTAGATGATGCTTGATCTAGATGAATGCGGACTTGCT  
GTAGCTAGATAAAATACAATGGGAGTTTGAAGGTGTTTCGTAGCCCTGGAA  
ATAGGTATTTCTGTCAAAACAAGCTTTGTCAATTGCCAGCAGACAAAAGC  
ATCAGTAACCTTGTTGATAATCGTCATTTCTTAGGAATAAAGTAGACT  
SG13S151

GTATTTCTGTCAAAACAAGCTTTGTCAATTGCCAGCAGACAAAAGC  
ATCAGTAACCTTGTTGATAATCGTCATTTCTTAGGAATAAAGTAGACTGT  
AGAATTTTTTTTAGCAGAAAGGAAACCCAAAGATAATTCTAGTGCAAATC  
CCTCACTTTATAGAGCAGAAGCTCAAGTCCCAGAGGAACAAGTGGCTTGA  
A[C/T]GAACATCAGAATTTTAGGGGCTGGATTTGTACCCTCCTGGTGCCAG  
CAGCCCCTTCCCTGCAGGAGGCACTCACCTTCCTTGACAGGGGTATGA  
GTGTGGCCATTTTCCACCCATAATCTCTGTAGCTCATGTTCAATTGGGTT  
CCCATTGAAAGAAAAATGGACCAGTAAGTTGGAGCAGAATCATTAGATG  
SG13S30

AGCTTTGTCAATTGCCAGCAGACAAAAGCATCAGTAACCTTGTTGA  
TAATCGTCATTTCTTAGGAATAAAGTAGACTGTAGAATTTTTTTTAGCAGA  
AAGGAAACCCAAAGATAATTCTAGTGCAAATCCCTCACTTTATAGAGCAG  
AAGCTCAAGTCCCAGAGGAACAAGTGGCTTGAACGAACATCAGAATTTTA  
G[G/T]GGCTGGATTTGTACCCTCCTGGTGCCAGCAGCCCCTTCCCTGCAG  
GAGGCACTCACCTTCCTTGACAGGGGTATGAGTGTGGCCATTTTCCACCC  
ATAATCTCTGTAGCTCATGTTCAATTGGGTTCCCATTTGAAAGAAAAATGG  
ACCAGTAAGTTGGAGCAGAATCATTAGATGGTATAACATAAGGAAAAA  
SG13S31

TGTTTAAATTGCTTTTATATCTGTAGCTCTAGATAAACACTAGTTCCA  
GCTTAGTTAACTCCCAGCTCCAAGCCTTCAGGACTTCATAGAGTTATTGGG  
GTGCTGCTCTTGGCAGTTTCCCAAAAAGCTAGAATGCAGAGGGAATCTCC  
TTCCCAAAAAGCTAGAATGCAGAGGGAATCTCCTTCCCAAAAAGGCTAGAA  
[C/T]GCAGAGGGAATCTCCTTCCCAAAAAGCTAGAATGCAGAGGGAATCT  
CCTTCCCAAAAAGGCTAGAACGCAGAGGGAATCTCCTTCCCAAAAAGGCTAG  
AACGCAGAGGGAATCTCCTTCCCAAAAAGGCTAGAATGCAGAGGGAATGT  
CCTTCTCTTCTAAATGGTAGCTGTTAGTTCAAGAAAGGTTAAACATTGTGC  
T  
SG13S152

GCTGCGTTTGCTGGACTGATGTACTTGTTTGTGAGGCAAAAAGTACT  
TTGTCGGTTACCTAGGAGAGAGAACGCAGAGGTAGGTAACTGGGACTACT  
AAAGAACTGTGGAGCGATTCTGATTTTGTAGCAGGAAGAGTGACAATTC  
AAAACAGTATTTGACTAGATTCACGGCTCCGTAGCATCCCCTTGGGTGGG  
AG[C/G]GGGAAGGCTGACTAGGACCTCTGATTCTTCTTCCCTGAGCTTTG  
AAGGCTCTGAAAATACAGCTGGGGGGACTTGCCAGTTTTCTTATTAAGC

FIG. 8.27

AATTCCTCCGCATGGTGCTGGCTTTCAAAGGGTGCTTCAGTGCTGTTTGCT  
GCACGTGCCTTGCAGCCCCACACCCTGCACTCCCGCCCTGCAGAGTCTGG  
C

SG13S402

GAGGCAAAAGTACTTTGTCTGGTTACCTAGGAGAGAGAACGCAGAG  
GTAGGTAACCTGGGACTACTAAAGAACTGTGGAGCGATTCTGATTTTGA  
GCAGGAAGAGTGACAATTCAAAACAGTATTTGACTAGATTCACGGCTCCG  
TAGCATCCCCCTTGGGTGGGAGGGGGAAGGCTGACTAGGACCTCTGATTCT  
TCT[C/T]TCCCTGAGCTTTGAAGGCTCTGAAAATACAGCTGGGGGGACTTG  
CCCAGTTTTCTTATTAAGCAATTCCTCCGCATGGTGCTGGCTTTCAAAGGG  
TGCTTCAGTGCTGTTTGCTGCACGTGCCTTGCAGCCCCACACCCTGCACTC  
CCGCCCTGCAGAGTCTGGCGCTGGAATGACATTTTAGGTCTGGGTTCCTCA  
G

SG13S403

TATCTTTCAGGGACCAGAAGAAAGAATGTTGGGAAAATAAGATGC  
AGTAAGATGCAGACATGACAGCAGGGTGACGCGGCTCACGCCTATAATCC  
CAGCACTTTGGGAGGCTGAGGTGGGTGGATCACCTGAGGTCAGGAGTTTG  
AGACCAGCCTGGCCAACATGGTGAAACCCCGTCTCTACTAAAAAATATAC  
AAA[A/G]CATTAGCCAGGCATGGTGGTGGGCGCCTGTAATCCCAGCTACTC  
CATAGGCTGAGGCTGGAGAATCGCTTGAACCCAGGAGGCAGAGGTTGCA  
GTGAGCCGAGATTGCGCCACTGCACTCCAGCCTGGGCAACAAAAGCAAA  
ACTCCATCTCAAAAAAAAAAAAAAAAAAAAAAAAAAAGATGCAGACACG  
AGACTG

SG13S153

TGGGCGCCTGTAATCCCAGCTACTCCATAGGCTGAGGCTGGAGAAT  
CGCTTGAACCCAGGAGGCAGAGGTTGCAGTGAGCCGAGATTGCGCCACTG  
CACTCCAGCCTGGGCAACAAAAGCAAACTCCATCTCAAAAAAAAAAAAAA  
AAAAAAAAAAAAAAAAAGATGCAGACACGAGACTGTGAACTGACTAGCAT  
CACC[A/T]TTGCATTGTTTATAGATGTTGCCAGACAGAAAGCCCCAAAGCA  
GCACAGTACCTTCCTGACATCTGGACTAGGAAATCTAGATTTTATAGTAAA  
TACATGCTAATACTTACAGAAGAAATGTCGGCGTTAGAGTATGCCGTCAG  
TTCTTAGAGATTGCAATTCCTAATGCACTAGTATGGTTTCAGGTGCCAGG  
AAC

SG13S97

ACTCCATCTCAAAAAAAAAAAAAAAAAAAAAAAAAAAGATGCAG  
ACACGAGACTGTGAACTGACTAGCATCACCATTGCATTGTTTATAGATG  
TTGCCAGACAGAAAGCCCCAAAGCAGCACAGTACCTTCCTGACATCTGGA  
CTAGGAAATCTAGATTTTATAGTAAAATACATGCTAATACTTACAGAAGAAA  
TGTC[A/G]GCGTTAGAGTATGCCGTCAGTTCCTTAGAGATTGCAATTCCTA  
ATGCACTAGTATGGTTTCAGGTGCCAGGAACACGTTCTGTGAGGCTGCTG  
CCCCAGGTGCTGACCCAGCCTTCCACACCATTTTCCTTCCTTGTGTTTAC  
AGCCGCTCTGTCTTTACAATAGCACCCCTCTCTAGTGGCTAATGGGCTCT  
AT

SG13S154

AAAAAAAAAAAAAAAAAAAAAAAAAAGATGCAGACACGAGACTGTGAA  
ACTGACTAGCATCACCATTGCATTGTTTATAGATGTTGCCAGACAGAAAG  
CCCCAAAGCAGCACAGTACCTTCCTGACATCTGGACTAGGAAATCTAGAT  
TTTAGTAAAATACATGCTAATACTTACAGAAGAAATGTCGGCGTTAGAGT  
ATGC[C/T]GTCAGTTCCTTAGAGATTGCAATTCCTAATGCACTAGTATGGTT  
TCAGGTGCCAGGAACACGTTCTGTGAGGCTGCTGCCCCAGGTGCTGACCC

FIG. 8.28

CAGCCTTCCACACCATTTTCCTTCCTTGTTTCACAGCCGCTCTGTCTTTTA  
CAATAGCACCCCTCTCTAGTGGCTAATGGGCTCTATGATTAGATAGCATCC  
SG13S40

TTTCAGGTGCCAGGAACACGTTCTGTGAGGCTGCTGCCCCAGGTGC  
TGACCCCAGCCTTCCACACCATTTTCCTTCCTTGTTTCACAGCCGCTCTGT  
CTTTTACAATAGCACCCCTCTCTAGTGGCTAATGGGCTCTATGATTAGATA  
GCATCCTTCAGTAGTGATAAAGGCAGTGACATCCTAGGGAGGTCAGCGG[  
G/T]TGAAAGCGCTATATCTGGAAAACCTGAGAGCCTGTGAAGCTCAAGGA  
CTTGACGGGGTTAGACCGTGAGCCGGGCTGCAGCTGGAAAAAGAATGACT  
GTTCTTTTCAGCATCCTTCCCTGTGCCATCTCTTTCTTCATTCCCTCTCTAG  
TGGCATTCTTATTTATCCTCTAAAACCACAATTCCATTATCTCTCCTA  
SG13S155

GAGGGTCTTCTCTTTTGCCTGGCTCCCTATGCAGCCCTATCTTACCC  
CCTGCAAAGTCCCAGGGATGTGGCTCAGTCACTGCTCCTCTCTTCATCTGT  
CACCATTGCTTGAGATCCTACAGCTGCTTTAATTCCGAGACCATCTGCAG  
AACATGACAAAATTTGTCCACCTACCCACATGTCTTTTAACTTTAAAG[A/  
G]CTTTACTAACTGATTCTTATTAGGGAATGAACAGAGGTGGCAAAAATAA  
ACAATAGGAGATTGATTTACAAGAAATCTTTAAAATAGTAGATTTCTTCG  
GACCTCATTGAAATATAAATGGCCTGCCTTCTTGTGTCCCTCCCTGGTCTC  
CCTCTTTAGGTGATAAGAAGAAGATCCTGCCAGCCCCATAACCCGCC  
SG13S156

TTAAAATAGTAGATTTCTTCGGACCTCATTGAAATATAAATGGCCT  
GCCTTCTTGTGTCCCTCCCTGGTCTCCCTCTTTAGGTGATAAGAAGAAGAT  
CCTGCCAGCCCCATAACCCGCCATCTGCGCGGGTTCTAGACCCCTTCTCC  
TCCCCTCTGGCCGTGGTAGGCATTACTGATGAATCATGGTGCTCTTTCTT[A/  
C]CAGAGACCAAACCTGGCCTCGGAATCCTTCTTAACACAGATACTGCTT  
AACACAACCACTCTGAGCAGCTGTCATAAGTAGAAGTAATAGATACTAGA  
AGAAATGTCTAAGCCTAATCTAGACCAAAAATACGGCCTGATATAGATGCA  
AGCCAGAGGGGCTTTATGGTTAAATGCAAGGAGATTTTCAACCCTGCCG  
SG13S157

CTGGTCTCCCTCTTTAGGTGATAAGAAGAAGATCCTGCCAGCCCCA  
TAACCCGCCATCTGCGCGGGTTCTAGACCCCTTCTCCTCCCTCTGGCCG  
TGGTAGGCATTACTGATGAATCATGGTGCTCTTTCTTCCAGAGACCAAACC  
TGGCCTCGGAATCCTTCTTAACACAGATACTGCTTAACACAACCACTCTG[  
A/G]GCAGCTGTCATAAGTAGAAGTAATAGATACTAGAAGAAATGTCTAAG  
CCTAATCTAGACCAAAAATACGGCCTGATATAGATGCAAGCCAGAGGGGCT  
TTATGGTTAAATGCAAGGAGATTTTCAACCCTGCCGTCTAGAAGCTACTTG  
CTGAGATCTTCTTCAGTTGGGCCCATCTCCTCCCCAGGCCTCTCTTCTG  
SG13S158

CCATAACCCGCCATCTGCGCGGGTTCTAGACCCCTTCTCCTCCCT  
CTGGCCGTGGTAGGCATTACTGATGAATCATGGTGCTCTTTCTTCCAGAGA  
CCAAACCTGGCCTCGGAATCCTTCTTAACACAGATACTGCTTAACACAAC  
CACTCTGAGCAGCTGTCATAAGTAGAAGTAATAGATACTAGAAGAAATGT  
[A/C]TAAGCCTAATCTAGACCAAAAATACGGCCTGATATAGATGCAAGCCA  
GAGGGGCTTTATGGTTAAATGCAAGGAGATTTTCAACCCTGCCGTCTAGA  
AGCTACTTGCTGAGATCTTCTTCAGTTGGGCCCATCTCCTCCCCAGGCCTC  
TCTTCTGTTCCTGGGCTATGTCACACTTGGACTCTGCAGACACCTAATGC  
SG13S159

TGGTAGGCATTACTGATGAATCATGGTGCTCTTTCTTCCAGAGACC  
AAACCTGGCCTCGGAATCCTTCTTAACACAGATACTGCTTAACACAACCA

FIG. 8.29

CTCTGAGCAGCTGTCATAAGTAGAAGTAATAGATACTAGAAGAAATGTCT  
AAGCCTAATCTAGACCAAAATACGGCCTGATATAGATGCAAGCCAGAGG  
GGC[G/T]TTATGGTTAAATGCAAGGAGATTTTCAACCCTGCCGTCTAGAAG  
CTACTTGCTGAGATCTTCTTCAGTTGGGCCCATCTCCTCCCCAGGCCTCTCT  
TCTGTTCTGGGCTATGTCACACTTGGACTCTGCAGACACCTAATGCTCTT  
GGGACCTGCTTTAGTTCTTGACCTACCAACCGAGGAGGAATTGCTAGAT  
SG13S160

CAGAGACCAAACCTGGCCTCGGAATCCTTCTTAACACAGATACTGC  
TTAACACAACCACTCTGAGCAGCTGTCATAAGTAGAAGTAATAGATACTA  
GAAGAAATGTCTAAGCCTAATCTAGACCAAAATACGGCCTGATATAGATG  
CAAGCCAGAGGGGCTTTATGGTTAAATGCAAGGAGATTTTCAACCCTGCC  
GT[C/T]TAGAAGCTACTTGCTGAGATCTTCTTCAGTTGGGCCCATCTCCTCC  
CCAGGCCTCTCTTCTGTTCCCTGGGCTATGTCACACTTGGACTCTGCAGACA  
CCTAATGCTCTTGGGACCTGCTTTAGTTCTTGACCTACCAACCGAGGAGG  
AATTGCTAGATGAGATCCTTCCCCCGGAATTTCTCTCTTGAACCCCA  
SG13S32

GGGCTTTATGGTTAAATGCAAGGAGATTTTCAACCCTGCCGTCTAG  
AAGCTACTTGCTGAGATCTTCTTCAGTTGGGCCCATCTCCTCCCCAGGCCT  
CTCTTCTGTTCCCTGGGCTATGTCACACTTGGACTCTGCAGACACCTAATGC  
TCTTGGGACCTGCTTTAGTTCTTGACCTACCAACCGAGGAGGAATTGCT[  
A/C]GATGAGATCCTTCCCCCGGAATTTCTCTCTTGAACCCCAAGATGGTCCG  
TTGCCCTTTCCAGAAGTTGCTCCAGCCCTGTCCGCTTAGGAAGTTCAAGT  
TCATCCTTGATCCAGTGGGTAGGGAAGACATTCCATAATGAATGCCCCAG  
TCTGAGCTTCTTCCCTCAGGCTTCAGGCTGCCCTGCGAGGATTTTGCA  
SG13S161

GTAGCTGAGACTACAGGTGTGCACTACCACACCCAGCTAATTTTTT  
GTATTTTATAGTAGAGATAGGGTTTAGCTATGTTGGCCAGGCTGGTCTCGAA  
CTGCTGAAGCAATCTGCCATCCCCGGCCTCCCAAAGTACTGGGAG  
TATAGGCATAAGCCACCCATGATGCCAGCCTGAATCTTGGTTTCTTCCCC  
[A/G]TTCATTTAAGCTATTACCTGGGCCTGAACTCAATGGCACCTGGCACC  
AACTGGCAACTGACTCTTGGTCTTTTATTACCTACCTTCCCTAGCAGGCAC  
TGGGTTGCTCCCTCTTCCCTATCCCATGGAGTCCTGTCTCTGTTGGGGCTCC  
TACTGATCCTCTTGGCAATATGAAGTTCTCAGCTCAATGGTGGGTG  
SG13S162

CCCGGCCTCCCAAAGTACTGGGAGTATAGGCATAAGCCACCCATG  
ATGCCAGCCTGAATCTTGGTTTCTTCCCCATTCAATTAAGCTATTACCTG  
GGCCTGAACTCAATGGCACCTGGCACCAACTGGCAACTGACTCTTGGTCT  
TTTATTACCTACCTTCCCTAGCAGGCACTGGGTTGCTCCCTCTTCCCTATCCC  
[A/G]TGGAGTCCTGTCTCTGTTGGGGCTCCTACTGATCCTCTTGGCAATAT  
GAAGTTCTCAGCTCAATGGTGGGTGGGCAATGACTGCCAACTCTTGAGGC  
CAATGAAGTCAAGGTTACCCCACTCCTCCTCCTGAGTTGCTCACTCACT  
CCTCATTCACTCAACATTGATTCAAGTAGATATTTGCTACCTGCTCTGT  
SG13S163

CCGGCCTCCCAAAGTACTGGGAGTATAGGCATAAGCCACCCATGAT  
GCCAGCCTGAATCTTGGTTTCTTCCCCATTCAATTAAGCTATTACCTGGG  
CCTGAACTCAATGGCACCTGGCACCAACTGGCAACTGACTCTTGGTCTTTT  
ATTACCTACCTTCCCTAGCAGGCACTGGGTTGCTCCCTCTTCCCTATCCCA[C  
/T]GGAGTCCTGTCTCTGTTGGGGCTCCTACTGATCCTCTTGGCAATATGA  
AGTTCTCAGCTCAATGGTGGGTGGGCAATGACTGCCAACTCTTGAGGCCA

FIG. 8.30

ATGAACTCAGGTTACCCCACTCCTCCTCCTGAGTTGCTCACTCACTCC  
TCATTCACCTCAACATTGATTAGTAGATATTTGCTACCTGCTCTGTG  
SG13S164

GGCATAAGCCACCCATGATGCCAGCCTGAATCTTGGTTTCTTCCC  
CATTCATTAAAGCTATTACCTGGGCCTGAACTCAATGGCACCTGGCACCAA  
CTGGCAACTGACTCTTGGTCTTTTATTACCTACCTTCCCTAGCAGGCACTG  
GGTTGCTCCCTCTTCTATCCCATGGAGTCCTGTCTCTGTTGGGGCTCC[C/  
T]ACTGATCCTCTTGGCAATATGAAGTTCTCAGCTCAATGGTGGGTGGGCA  
ATGACTGCCAACTCTTGAGGCCAATGAACTCAGGTTACCCCACTCCTCCTC  
CTCCTGAGTTGCTCACTCACTCCTCATTCACTCAACATTGATTAGTAGAT  
ATTTGCTACCTGCTCTGTGCCAGGTACCAGGTCAGTTGCTGAAGGA  
SG13S165

CCTGGCACCAACTGGCAACTGACTCTTGGTCTTTTATTACCTACCTT  
CCCTAGCAGGCACTGGGTTGCTCCCTCTTCTATCCCATGGAGTCCTGTCC  
TCTGTTGGGGCTCCTACTGATCCTCTTGGCAATATGAAGTTCTCAGCTCAA  
TGGTGGGTGGGCAATGACTGCCAACTCTTGAGGCCAATGAACTCAGGTT[A/  
T]CCCCACTCCTCCTCCTGAGTTGCTCACTCACTCCTCATTCACTCAAC  
ATTGATTAGTAGATATTTGCTACCTGCTCTGTGCCAGGTACCAGGTCAGT  
TGCTGAAGGAGTAACAGTGAACATGACGGAGTCTTTGTCCCCAAGGAGAC  
CCAAGGTGTCTCCTAGAGCCAGGGGCACATTGCAAGACCAAATATA  
SG13S166

CTGGCAACTGACTCTTGGTCTTTTATTACCTACCTTCCCTAGCAGGC  
ACTGGGTTGCTCCCTCTTCTATCCCATGGAGTCCTGTCTCTGTTGGGGC  
TCTACTGATCCTCTTGGCAATATGAAGTTCTCAGCTCAATGGTGGGTGGG  
CAATGACTGCCAACTCTTGAGGCCAATGAACTCAGGTTACCCCACTCCT[C/  
T]CTCCTCCTGAGTTGCTCACTCACTCCTCATTCACTCAACATTGATTAGT  
AGATATTTGCTACCTGCTCTGTGCCAGGTACCAGGTCAGTTGCTGAAGGA  
GTAACAGTGAACATGACGGAGTCTTTGTCCCCAAGGAGACCCAAGGTGTC  
TCCTAGAGCCAGGGGCACATTGCAAGACCAAATATATTCAACTTACC  
SG13S167

CCATGGAGTCCTGTCTCTGTTGGGGCTCCTACTGATCCTCTTGGCA  
ATATGAAGTTCTCAGCTCAATGGTGGGTGGGCAATGACTGCCAACTCTTG  
AGGCCAATGAACTCAGGTTACCCCACTCCTCCTCCTGAGTTGCTCACT  
CACTCCTCATTCACTCAACATTGATTAGTAGATATTTGCTACCTGCTCT[A/  
G]TGCCAGGTACCAGGTCAGTTGCTGAAGGAGTAACAGTGAACATGACGG  
AGTCTTTGTCCCCAAGGAGACCCAAGGTGTCTCCTAGAGCCAGGGGCACA  
TTGCAAGACCAAATATATTCAACTTACCAAAATAATCATAGACCTAGTTCT  
CAAAAAGCAAGAAGACTGATTCTCGTTGTCATTTCTCCTCCTCAGCA  
SG13S168

TTAGAGTCTGTGGGCCCCCTCCAAGTGTGGAGTATGGTGTACTTCA  
CCAGAGTTTGAGGAGAAACATTCTTCTTTTGGGAAGGCCGGGGAGCATAGA  
TGGATATCAAGGCTGCTGTTTCTAAAAGCGAAACCCACCAAACAACAGTA  
TTAGAATCATCTGTGGTGCTTATTAAGATACAGATTCTTGGGCCCCATCC  
C[A/C]GACTTATGAATCAGAATCTCTGCCAGAGGAAGCCTGAGAATTTGCA  
TTCTCAGATGATTCTGCATTCTCAGATAACACATTCTTTAGGTGATTCTTAC  
ACACACTGGAGTTTGGGAATCGCTGAAGGCTGTTCACTTCTCTTTTCTGAG  
AAATGATTCAATTCATTTCAGAAATATTTGCAGAGGTCCTTATTTATTG  
SG13S33

TGGCCTCATTCGTGTGATAAATCTGAGCCACCACGATATTTGACTTT  
TCACAATTTAATTTATCTGAACCCTCTATTCTCTGGCTAAAAAATATCCCT

FIG. 8.31

TACTTGGACTTCTTTATTTTATTTTCAATTCCCTTACCAGCACTAGCAGGGG  
ACTCTGTACTCATCTGCTGGCGCTGCCATAACAAAGCACTGCAGCCTG[G/T  
]GGGGCTCAAACACAGAATTTATTCTCTCACAGTCCTAGAGGCTAGAAGT  
CCAAGATCAAAGTGTGGGCAGGGTCGGTTTCTCCTGCAGCCTCTCTCCTTG  
GCTTATAGAGTGCCACCTTCTACCTGTGTCTTCACATCATCACCTCACTGA  
GCATGTCTGTGTCCAAATCTCCCCTTCTTATAAGACCCCAGTCAT  
SG13S41

TCTCCTTGGCTTATAGAGTGCCACCTTCTACCTGTGTCTTCACATCA  
TCACCTCACTGAGCATGTCTGTGTCCAAATCTCCCCTTCTTATAAGACCCC  
AGTCATACTGGATGAGGATCCACCCATATGAGTTCATTTTACCTTAATTAT  
CTCTTTAAACACCCTGTCTCCAAATACAGTCCCATTCTGAGGAACTGAG[A/  
G]GTAAAGATTCAACATATGAATTTTGGAAAGGGACCTAATTCAGCCCACA  
ACACCCTCTTTTGGGATGTTTATTTTCCCCCTTAAGGAGCTAGTTAGGATG  
TCTTATCTCATGAACATGACTGTGAACAGGAAAACAGGGAGAGAATGAA  
GCTGGCCAAGGAACAGGGCTGGTGTGCTAGCAGTGCTTTTCTGATGT  
SG13S169

CATTTTACCTTAATTATCTCTTTAAACACCCTGTCTCCAAATACAGT  
CCCATTCTGAGGAACTGAGAGTAAAGATTCAACATATGAATTTTGGAAAGG  
GACCTAATTCAGCCCACAACACCCTCTTTTGGGATGTTTATTTTCCCCCTT  
AAGGAGCTAGTTAGGATGTCTTATCTCATGAACATGACTGTGAACAGGAA[  
A/G]ACAGGGAGAGAATGAAGCTGGCCAAGGAACAGGGCTGGTGTGCTAGCT  
AGCAGTGCTTTTCTGATGTGAGTGGGTCCACAGGGAGCTTGTTAAATG  
CAGATTCTGATTCAATTAGGTTCCAGAGGGACCTGAGATTTCCCATTTCTGA  
CAAGTTTCCAGTGTGGGGGCTGATGCTGCTGGTCCACGGACCATACTTTG  
SG13S404

GGGAGAGAATGAAGCTGGCCAAGGAACAGGGCTGGTGTGCTAGCTAG  
CAGTGCTTTTCTGATGTGAGTGGGTCCACAGGGAGCTTGTTAAAAATGCA  
GATTCTGATTCATTAGGTTCCAGAGGGACCTGAGATTTCCCATTTCTGACA  
AGTTTCCAGTGTGGGGGCTGATGCTGCTGGTCCACGGACCATACTTTGAGT  
A[G/T]CAAGGAGCTTGATACATAATGGCTGAGTGACTTTCAGACTCCTGCT  
GTAGAAAAATTATGAGTTGGCTGGGCGTGGTGGCTCACGCCTGTAATCCC  
AGCACTTTGGGAGGCCGAGGTGGGCAGATCACCTGAGGTCAGGAGTTCTGA  
GACCAGCCTGGCCAACATGGTGAAACACCATCTCTACCAAAAATACAAAA  
A  
SG13S170

ACTTAAGCCCAGAAGACTGAGGTTGCAGTGAGCCGAGATTGCACC  
ACTGCACTCCAGCTTGGGCTACAGAGTGAGACTCTATCTCAAAAACAAAG  
AAACAAACAACAATAACAACAAAAACCAAGTCTCTCCCTCCACTCAA  
AAATGCAAGGGCCTGTCTCCCATTTGCTGGGTGCCAGGTCTCATGAATGT  
AGA[C/T]ATGAATTATTCCAGTCAGCCTCAGGAGAATAGAATGAGCCCTCA  
GATGCCGAAGCACCTTTCAGATTCCACCGGTTTTATCGGCTCATTTAACT  
TCACTTCTAACACAGTCCTGCATTACACACGTGTCTGTCGTTATGGGCAGC  
TGCAGAGAGGGTCTTAATGGTCCTAATGCTCAGTGAGGATGCCCAATGGT  
C  
SG13S171

CTCAAAAACAAAGAAACAACAACAACAATAACAACAAAAACCA  
AGTCTCTCCCTCCACTCAAAAATGCAAGGGCCTGTCTCCCATTTGCTGGGTG  
CCCAGGTCTCATGAATGTAGATATGAATTATTCCAGTCAGCCTCAGGAGA  
ATAGAATGAGCCCTCAGATGCCGAAGCACCTTTCAGATTCCACCGGTTTT  
ATC[A/G]GCTCATTTAACTTCACTTCTAACACAGTCCTGCATTACACACGT

FIG. 8.32

GTCTGTCGTTATGGGCAGCTGCAGAGAGGGTCTTAATGGTCCTAATGCTC  
AGTGAGGATGCCCAATGGTCAACAGAACCTGCCATCTTCAGGCCATCAAG  
GAGCTCTGGAGTTAAGGAAATCATGAGAGCACAGAGGGGGCGGGTACAGC  
AGA

SG13S172

TGTAGATATGAATTATTCCAGTCAGCCTCAGGAGAATAGAATGAGC  
CCTCAGATGCCGAAGCACCTTTCAGATTCCACCGGTTTTATCGGCTCATTT  
AAACTTCACTTCTAACACAGTCCTGCATTACACACGTGTCTGTCGTTATGG  
GCAGCTGCAGAGAGGGTCTTAATGGTCCTAATGCTCAGTGAGGATGCCCA  
[A/G]TGGTCAACAGAACCTGCCATCTTCAGGCCATCAAGGAGCTCTGGAGT  
TAAGGAAATCATGAGAGCACAGAGGGGGCGGGTACAGCAGAGCCCTCGTG  
GTAATGGGTTTTGAGGTCTAGGCTCTCTTCACTTGGGTTTGAAATAAGTTC  
AATGACTAGTAATAGCTGAGACACTTCTACCCTTCAAATGAAGTAAATGG  
SG13S173

AGCACCTTTCAGATTCCACCGGTTTTATCGGCTCATTTAACTTCAC  
TTCTAACACAGTCCTGCATTACACACGTGTCTGTCGTTATGGGCAGCTGCA  
GAGAGGGTCTTAATGGTCCTAATGCTCAGTGAGGATGCCCAATGGTCAAC  
AGAACCTGCCATCTTCAGGCCATCAAGGAGCTCTGGAGTTAAGGAAATCA  
[A/T]GAGAGCACAGAGGGGGCGGGTACAGCAGAGCCCTCGTGGTAATGGGT  
TTTGAGGTCTAGGCTCTCTTCACTTGGGTTTGAAATAAGTTCAATGACTAG  
TAATAGCTGAGACACTTCTACCCTTCAAATGAAGTAAATGGGAAAATGGA  
GCATTGTTGAGTCCAGGGAGCTATAATTTAAACCCCATATATCTAAAAGG  
SG13S42

CACACGTGTCTGTCGTTATGGGCAGCTGCAGAGAGGGTCTTAATGG  
TCCTAATGCTCAGTGAGGATGCCCAATGGTCAACAGAACCTGCCATCTTC  
AGGCCATCAAGGAGCTCTGGAGTTAAGGAAATCATGAGAGCACAGAGGG  
GCGGGTACAGCAGAGCCCTCGTGGTAATGGGTTTTGAGGTCTAGGCTCTC  
TTC[A/G]CTTGGGTTTGAAATAAGTTCAATGACTAGTAATAGCTGAGACAC  
TTCTACCCTTCAAATGAAGTAAATGGGAAAATGGAGCATTGTTGAGTCCA  
GGGAGCTATAATTTAAACCCCATATATCTAAAAGGGGTAACATTTTTGTGT  
GTGTGAAATTGGTGTCATTTCGCACTGCATCTACAGTTTTCTTTTTCTTCTC  
SG13S194

ACATATTTGGGAAACGCATCATACTCTTCCTGTTCCCTCATGTCCGTT  
GCTGGCATAATCAACTATTACCTCATCTTCTTTTTCCGAAGTGACTTTGAA  
AACTACATAAAGACGATCTCCACCACCATCTCCCTCTACTTCTCATTTCCC  
TAACTCTCTGCTGAATATGGGGTTGGTGTTCTCATCTAATCAATACCTA[C/  
T]AAGTCATCATAATTCAGCTCTTGAGAGCATTCTGCTCTTCTTTAGATGGC  
TGTAATCTATTGGCCATCTGGGCTTCACAGCTTGAGTTAACCTTGCTTTT  
CCGGGAACAAAATGATGTCATGTCAGCTCCGCCCCTTGAACATGACCGTG  
GCCCCAAATTTGCTATTCCCATGCATTTTGTTTGTTTCTTCACTTA  
SG13S195

TGGTGTTCTCATCTAATCAATACCTACAAGTCATCATAATTCAGCTC  
TTGAGAGCATTCTGCTCTTCTTTAGATGGCTGTAAATCTATTGGCCATCTG  
GGCTTCACAGCTTGAGTTAACCTTGCTTTTCCGGGAACAAAATGATGTCAT  
GTCAGCTCCGCCCCTTGAACATGACCGTGGCCCCAAATTTGCTATTCCC[A/  
G]TGCATTTTGTTTGTCTTCACTTATCCTGTTCTCTGAAGATGTTTTGTGA  
CCAGGTTTGTGTTTTCTTAAATAAAATGCAGAGACATGTTTTAAGCTGAT  
AGTTGAGGGGTTTTGTTAATGGCTTTTGGGGGATTTATCTCTATACCCACA  
AACGACTAGTTTGTTTTCTCAAACATAAATGATAATATTAATAA

FIG. 8.33

SG13S174

TTATCTCTATACCCACAAACGACTAGTTTGTTCCTCAAACCTAAAT  
GATAATATTAATAACACATCCTGGCCAGGTGTGGTGGCTCATACCTGT  
AATCCCAGCACTTTGGGAGGCCGAGGCAGGTGGATCACTTGAGGTCAGGA  
ATTAAGACCAGCCTGGCCAATATGGTGAAAGCCTGTCTGTACTAAAAATA  
C[A/G]AAAATTAGCCAGGTATGCTGGTGGATGCTTATAATCCCAGCTACTT  
GGGAGGTTGAGGCAGGAGAATTGCTTGAACCCGGGAGGTAGAGGTTGCA  
GTGAGCCAAGATCATGCCACTGCACTCCAGCTTGGGCAACAGAGTGAGAC  
TCCATCTCAAATTAATAAAAAAATACACATCTGGCTTCTGGAAAAATTACTT  
GA

SG13S34

GATCATGCCACTGCACTCCAGCTTGGGCAACAGAGTGAGACTCCAT  
CTCAAATTAATAAAAAAATACACATCTGGCTTCTGGAAAAATTACTTGAAGA  
TCTTTTATGACATCCATCCCTCTTCACACAGCCATGTGAATTAGGTTGGTA  
TCTTCATATACTAGCATCGTGCCCAAGCACTTCCATGTTATACAGTTTAAAAA[  
G/T]GTTCTGTAATTCCTGTGGGAACCTAAGATAATGCGAGGACCGTCAT  
ACGTGCCCCCAAATATTGGCAAACCAATGAATAAATGAATGAATGAGTTT  
ATGAATCGCTAACTGGCTGTATTTAATGAAGTATGTGTGTTGAGCCATTTT  
CCACAGTGTGGACAGATTTGTCCCAATATGGGCCTCTTCCCAAAGGC

SG13S175

AATTAATAAAAAAATACACATCTGGCTTCTGGAAAAATTACTTGAAGA  
TCTTTTATGACATCCATCCCTCTTCACACAGCCATGTGAATTAGGTTGGTA  
TCTTCATATACTAGCATCGTGCCCAAGCACTTCCATGTTATACAGTTTAAAA  
TGTTCTGTAATTCCTGTGGGAACCTAAGATAATGCGAGGACCGTCATAC[  
A/G]TGCCCCCAAATATTGGCAAACCAATGAATAAATGAATGAATGAGTTT  
ATGAATCGCTAACTGGCTGTATTTAATGAAGTATGTGTGTTGAGCCATTTT  
CCACAGTGTGGACAGATTTGTCCCAATATGGGCCTCTTCCCAAAGGCC  
CTACCACCTAATGCCATCACACTGGGGATTTGATTTCAACATGTGAATT

SG13S176

AGTTCATAGTGACAGTGATCCAGCCACTGTCATGACAGGTGCCACT  
TGGCAGAAACAGCACAGCTTGGGAAGATGGCGGGGTGTAGTCAAGATTCC  
AGGATCCCCAACAGAGAAGCCAGCTCTTATAGGGGAGCCATTCATCAGGA  
TTGAACTCTCAATCGAGCTGGACAGTAATAGGTGGGTCTGTGTTATTCCCC  
AG[A/G]TGAGTATCATGACAGTCACAATCCTAGGAAGGATGTGAAGCCTC  
CCCCAGCTCTCCTCCAGTTGCCTGCTTGGGCAGCAGAGATGATGGAATGT  
GGAGTCTGGCGTGGTCTGAGGCCTGAATCCATGTGCCTCATGTATGATGCT  
CAGGCAAGAGGATCTCTCAATTCAAGGGAGAGGGCCTGAATGAGCCTTGC  
TT

SG13S177

CTTGGCAGAAACAGCACAGCTTGGGAAGATGGCGGGGTGTAGTCAA  
GATTCCAGGATCCCCAACAGAGAAGCCAGCTCTTATAGGGGAGCCATTCA  
TCAGGATTGAACTCTCAATCGAGCTGGACAGTAATAGGTGGGTCTGTGTT  
ATTCCCCAGATGAGTATCATGACAGTCACAATCCTAGGAAGGATGTGAAG  
CCT[C/T]CCCCAGCTCTCCTCCAGTTGCCTGCTTGGGCAGCAGAGATGATG  
GAATGTGGAGTCTGGCGTGGTCTGAGGCCTGAATCCATGTGCCTCATGTA  
TGATGCTCAGGCAAGAGGATCTCTCAATTCAAGGGAGAGGGCCTGAATGA  
GCCTTGCTTTCCAGGCCTGTCTGATGGTCCAGGCTGAAGCCCCCTCCTGGCT  
TG

SG13S178

CTGGCGTGGTCTGAGGCCTGAATCCATGTGCCTCATGTATGATGCT

FIG. 8.34



CAGGCAAGAGGATCTCTCAATTCAAGGGAGAGGGCCTGAATGAGCCTTGC  
TTTCCAGGCCTGTCTGATGGTCCAGGCTGAAGCCCCTCCTGGCTTGCACCTG  
CCAGACCTCATCCAGCAGGAGCTCCTTGGCATTGACTGCTTCAGGATAGTT  
[C/G]CTTCTGCTCTGAGTGCTCTCTAAAGAGCAGTGCTCTACCATCCAAGC  
TGGGCTTTTCTTTCTTCTTGCTGATAGGGAAGGCATGGGACATTGCAGGA  
TGGAAGTGGCCCCCAGGCCTTCTCATGCCTGGGCTTGGTTTGAAGGTGG  
TCAGGTGATCAATAATCCTGATTGGCCTGGCATTGAGGAGTTTCTCTGG  
SG13S35

TGCTCTCTAAAGAGCAGTGCTCTACCATCCAAGCTGGGCTTTTCTTT  
TCTTCTTGCTGATAGGGAAGGCATGGGACATTGCAGGATGGAAGTGGCCC  
CCAGGCCTTCTCATGCCTGGGCTTGGTTTGAAGGTGGTCAGGTGATCAAT  
AATCCTGATTGGCCTGGCATTGAGGAGTTTTCCTGGGATGTGGTCCTTTC[A  
/G]GTTTTTTAAAAATTATTTTTATTGATACACATATTTGTAGGTATTTGTGG  
GGTGCATGTGATACTTTATTATGTGTGTGGATTGTGTAATGATGAAGTCAG  
GGCATTAGGGTCTTCATCACCTTGATTATCATTTCTATGTGTTGAGAACA  
TTTCAAGTTCTCAGTTCAGCTATTTTGAAATAGACAGTCCATTT  
SG13S179

GATACTTTATTATGTGTGTGGATTGTGTAATGATGAAGTCAGGGCA  
TTTAGGGTCTTCATCACCTTGATTATCATTTCTATGTGTTGAGAACATTTCA  
AGTTCTCAGTTCAGCTATTTTGAAATAGACAGTCCATTTTGTAGCTACA  
GTCACCCAACCCGGCTGTGACACATTGGAACCTACTCCTATTGAACTGT[A/  
G]TATTTGTACCCATTACCAAACCTCTCTTTGGGCTTTCAGTTTTACAACCTG  
GGATGATCCTGGGAAAACATAAAGTAAATCAGACACCCGACGTGTGAGCTA  
GGTTATAATATGCCAGTGGACCCTGGGGACATCTTAGCTTTCAGAGGTC  
ATGCTGTCCAAGCTGACTGTGGGGCTTCCAGAAGGTGGGGAGAGGAA  
SG13S180

TATGTGTGTGGATTGTGTAATGATGAAGTCAGGGCATTTAGGGTCT  
TCATCACCTTGATTATCATTTCTATGTGTTGAGAACATTTCAAGTTCTCAGT  
TCCAGCTATTTTGAAATAGACAGTCCATTTTGTAGCTACAGTCACCCAAC  
CCGGCTGTGACACATTGGAACCTACTCCTATTGAACTGTGTATTTGTAC[C/  
T]CATTCACCAAACCTCTCTTTGGGCTTTCAGTTTTACAACCTGGGATGATCCT  
GGGAAAACATAAAGTAAATCAGACACCCGACGTGTGAGCTAGGTTATAATA  
TGCCAGTGGACCCTGGGGACATCTTAGCTTTCAGAGGTCATGCTGTCCA  
AGCTGACTGTGGGGCTTCCAGAAGGTGGGGAGAGGAAATGATGCAAT  
SG13S181

TGGGAAAACATAAAGTAAATCAGACACCCGACGTGTGAGCTAGGTT  
ATAATATGCCAGTGGACCCTGGGGACATCTTAGCTTTCAGAGGTCATGC  
TGTCCAAGCTGACTGTGGGGCTTCCAGAAGGTGGGGAGAGGAAATGATGC  
AATGGCCCATCAGAGGCACTACTTGGGGCCTGGGGCCAGAGTGCATGTCT  
AAG[C/G]CATTAAAGGGGAGGGGAGAGCAGCCTTCATAATTATGAAGAGGA  
GTCTCAGGTGCACAGCTTCTGATGAGGGACAGCTTCTAATTGAAGACAGC  
ATTGTGTAATGCTCAAACCTCCCTGTCTTCAGAGTGCCTGCTGTATCCCACC  
ATCAGTTCTGTGACTTCTCCCTAAGCCTCAATTTTGCATGTGTTACATTGG  
GA  
SG13S182

CCTGCATAGCAAATTCTTGCAAATGTAGGGACTCAAAACAATATAA  
ATTTATTATCTGACAGTTTTTCTGGGTCAGAGGTCTTACTAGGCTGTAATC  
AGAGGGCAACCAAAGCTGTGATCTCAGCTGAAGCTCAGGATTCTCTTCCA  
AGCTCACTGGTTGTTGGCAGAATTCAGTTCTTTCCAGTTGGAAGACTAAAG  
[C/T]CTACAGTCTTCAGTCTCTAGAAGCCTTTTCTCTGGCACAGGTTTCTCT

FIG. 8.35

ACAACATGGCCATTTATGTCTTTAAGGCCAATAGGAGAACATGATTAGCA  
TATTTTTTTTAAAGTGAACCTTTAGACCCTTTTTTAAAGGCCTATCTGATTAGG  
CCAGGCCCAAGTGAGCTTTAAGTCAACTGATTAGAGATCTTAATTAC  
SG13S183

CTGAAGCTCAGGATTCTCTTCCAAGCTCACTGGTTGTTGGCAGAAT  
TCAGTTCTTTCCAGTTGGAAGACTAAAGCCTACAGTCTTCAGTCTCTAGAA  
GCCTTTTCTCTGGCACAGGTTTCTCTACAACATGGCCATTTATGTCTTTAA  
GGCCAATAGGAGAACATGATTAGCATATTTTTTTTAAAGTGAACCTTTAGAC[  
C/T]CTTTTTTAAAGGCCTATCTGATTAGGCCAGGCCCAAGTGAGCTTTAAG  
TCAACTGATTAGAGATCTTAATTACATCTGCAAAGTCCCTTCATGTTTACC  
GTATAACATAACTTAGTGAAAGGAGTGAAATTGCAACCAGGTTCTGCCTG  
CACTCCACGGAAGGGGATTCTGCAGAAGTGTGGGTACGGGGGGGGTTA  
SG13S184

AGAACATGATTAGCATATTTTTTTTAAAGTGAACCTTTAGACCCTTTTT  
TAAAGGCCTATCTGATTAGGCCAGGCCCAAGTGAGCTTTAAGTCAACTGA  
TTAGAGATCTTAATTACATCTGCAAAGTCCCTTCATGTTTACCGTATAACA  
TAACCTAGTGAAAGGAGTGAAATTGCAACCAGGTTCTGCCTGCACTCCAC[  
A/G]GAAGGGGATTCTGCAGAAGTGTGGGTACGGGGGGGGTTATTTTGGGA  
TTCTGCCTACGTCACTGAGTCAAAAGAAGCTGAATGGTTGTGATGCTGAG  
GTTTTTGGGCAGCAGCAGTGTGTGTGTGTGAGTGAATTCATACGTATGACC  
ACCTGGGAAGAAAGGAGGCTGTGGTTTCCTCCACCTCCTGGCAGACAGA  
SG13S185

GGGATTACAGACACACACTGCCACGCCTGGCTAATTTTTGTATTTTT  
AGTAGAGACGAGGTTTTGCCATGTTGGCCAGGCTGGTCTTGAACCTCCTGA  
CCTCAAGTGATCCGCCCACCTCAGCCTCCCAAAGTGCTGGGATTACAGAC  
GTGAGCCACCATTAACCATTTTTCTATCTCCTGTGGGAAAGGGCACAGTG  
A[A/G]AGAACAGATGAAGCTGAGACATACAAGTGAACCTCCTCCCTCCTCTC  
CATTTAGACTAAAATAGGATTATTCATACTGAGATTCTCCCTGGTTGCAAA  
GAGATAATCTGTGCAACTGGGTTTTTACAATTATCCCTACCCTATGCTTTC  
CTCATCTGTCTTCCTCGTAGTCAGCTCAGGCTGCTATAACAAAACACCA  
SG13S405

GGCAGATTCCGGTGTCTAATGAGGTCCTGCTTTCCAGTTTATAGACA  
GTGCCTTATCGCTACCGCCTTACACAGTGGAAGGAGAGGACGAGAAGCTC  
CTTGGGCTTTTTTTTTGTTTCTTTCTTTCTCTCTCTCTTTTTTTTTTTTT  
AATAAGGTCATATCTTAGTCCATTTTGTGTTGCTAAAAGGAACATCT[A/G  
]AGGTTGAGTAATTTATTTTATTTTAAAAAGTGGCCAGGCATGGAGGCTTA  
TCCTGTAACCCTAATCCTTTAGGAGGCCAAAACAGCAGGATTGTTTGAGG  
CCAGGAGTTCAAGACCAGCCTAGGCAAGATAGTGAGACCCCATCTACCCC  
ATCTCTACTAAAATTTTAAAAAATTAGCTGTGTGTTGTAAAGTGTGC  
SG13S91

AATTTATTTTATTTTAAAAAGTGGCCAGGCATGGAGGCTTATCCTGT  
AACCTAATCCTTTAGGAGGCCAAAACAGCAGGATTGTTTGAGGCCAGGA  
GTTCAAGACCAGCCTAGGCAAGATAGTGAGACCCCATCTACCCCATCTCT  
ACTAAAATTTTAAAAAATTAGCTGTGTGTTGTAAAGTGTGCTTGTAGTCCC  
[A/G]GCCACTTGAGAGGCTGAGGTGGGTGGAGTTCAAGGCTGCAGTGAGT  
TATGATTGAGCCACTGCACTCCAACCCGGGTAAACGGGGCAAGACCTTGTC  
TCTATTTAAAAAATAAATCTTTATGTGGCTCACTATTCTGGGTGGCTGG  
AAAGTTCAAGATTGGGCATCTGCATCTGGTGACAGCCTCATGTGCTTCC  
SG13S186

TAACCCTAATCCTTTAGGAGGCCAAAACAGCAGGATTGTTTGAGGC

FIG. 8.36

CAGGAGTTCAAGACCAGCCTAGGCAAGATAGTGAGACCCCATCTACCCCA  
TCTCTACTAAAATTTTAAAAAATTAGCTGTGTGTTGTAAAGTGTGCTTGTA  
GTCCCGGCCACTTGAGAGGCTGAGGTGGGTGGAGTTCAAGGCTGCAGTGA  
G[A/T]TATGATTGAGCCACTGCACTCCAACCCGGGTAAACGGGGCAAGACCT  
TGTCTCTATTTAAAAAATAATCTTTATGTGGCTCACTATTCTGGGTGG  
CTGGAAGATTCAAGATTGGGCATCTGCATCTGGTGACAGCCTCATGTGCGC  
TTCCAGTCATGGGGGAAGACGAAGGAGAGCTGGCACGTGCAGATATCAC  
G

SG13S187

ATCCTTTAGGAGGCCAAAACAGCAGGATTGTTTGAGGCCAGGAGTT  
CAAGACCAGCCTAGGCAAGATAGTGAGACCCCATCTACCCCATCTCTACT  
AAAATTTTAAAAAATTAGCTGTGTGTTGTAAAGTGTGCTTGTAAGTCCC  
CACTTGAGAGGCTGAGGTGGGTGGAGTTCAAGGCTGCAGTGAGTTATGAT  
T[A/G]AGCCACTGCACTCCAACCCGGGTAAACGGGGCAAGACCTTGTCTCTA  
TTAAAAAATAATCTTTATGTGGCTCACTATTCTGGGTGGCTGGAAA  
GTTCAAGATTGGGCATCTGCATCTGGTGACAGCCTCATGTGCGCTTCCAGTC  
ATGGGGGAAGACGAAGGAGAGCTGGCACGTGCAGATATCACGTGTTGAG  
G

SG13S188

TTAAAAAATTAGCTGTGTGTTGTAAAGTGTGCTTGTAAGTCCC  
ACTTGAGAGGCTGAGGTGGGTGGAGTTCAAGGCTGCAGTGAGTTATGATT  
GAGCCACTGCACTCCAACCCGGGTAAACGGGGCAAGACCTTGTCTCTATTT  
AAAAAATAATCTTTATGTGGCTCACTATTCTGGGTGGCTGGAAAGTT  
CA[A/G]GATTGGGCATCTGCATCTGGTGACAGCCTCATGTGCGCTTCCAGTC  
ATGGGGGAAGACGAAGGAGAGCTGGCACGTGCAGATATCACGTGTTGAG  
GGCAGAAGCGAGAGAGAGAGGGGAGAGATGCCAGGCTCTTTTAAACAAC  
CAGCACTGGGGAACTAATAGAGTGAGAGCTCACTGACTCCTGAGGGAG  
GACAT

SG13S406

ATGGGGGAAGACGAAGGAGAGCTGGCACGTGCAGATATCACGTGT  
TGAGGGCAGAAAGCGAGAGAGAGAGGGGAGAGATGCCAGGCTCTTTTAA  
CAACCAGCACTGGGGAACTAATAGAGTGAGAGCTCACTGACTCCTGAGG  
GAGGACATTAATCTATTGATGAGCGACCTGCCTCCATGACCCAAACACCT  
CCAA[C/T]GATACCCACCTCCAACACTGCCACACTAGGGATTAACTTTCA  
ACTTGAGATTTAGAGGGGGGAACTTACAAACTATCGCAGGGCACTAATAC  
CACTCATGAGGGCTCCACCTTCATGACCTAATCACTTCCTAAAGGCCTTAC  
CTCTTAATCTCATCACATTGAGGATTCGATTTCAACTTGAATTTTGGGGGG  
AC

SG13S92

CTCGCTGCCACCTGAAATTAGATCATTTATTTACCCCTTTATTTGTT  
CAGTTTGCCTTGTCCGTTAGAATATAAGCTTCCAAAGGGCAGGAGCTTGC  
CTATATTGTTAGGCCGGGCATACAATGAGCACTCAAAAAAATATTTGATG  
AGTGTATGAAAGAACAGACTGGGTTATGTAATTGTGCCTACTTACCTATA[  
C/T]GACCGTGTGGTGGGGTTTATGGTGGGTGTGGTGGTGTGATGGCTATAGG  
GCTATAAGCAAATTTGGGACAGGGAGTCTAAGAAATGTTCTTAAATTTTA  
GTAAGCAAAGCATCCTCTACAGAACCTGTCTTAAACATGAAAGTTTCTT  
AGTGCTACCCCCAGAGGTATGATTTGGTAGGTCAAGGATAGGGCCTGGAA  
SG13S93

TGCCACCTGAAATTAGATCATTTATTTACCCCTTTATTTGTTTCAGTT  
TGCCTTGTCCGTTAGAATATAAGCTTCCAAAGGGCAGGAGCTTTCCTATA

FIG. 8.37

TTGTTAGGCCGGGCATACAATGAGCACTCAAAAAAATATTTGATGAGTGT  
ATGAAAGAACAGACTGGGTTATGTAATTGTGCCTACTTACCTATATGACC[  
A/G]TGTGGTGGGGTTTATGGTGGGTGTGGTGGTGATGGCTATAGGGCTAT  
AAGCAAATTTGGGACAGGGAGTCTAAGAAATGTTCTTAAATTTTAGTAAG  
CAAAGCATCCTCTACAGAACCTGTCTTAAACATGAAAGTTCCTTAGTGCT  
ACCCCAGAGGTATGATTTGGTAGGTCAAGGATAGGGCCTGGAAATTCA  
SG13S36

CCTGTCTTAAACATGAAAGTTCCTTAGTGCTACCCCCAGAGGTAT  
GATTTGGTAGGTCAAGGATAGGGCCTGGAAATTCACATTCTTGTTAAGAT  
GTTCTTCATCCGGGGTTTGTTGACCACCTTTTCAGAAGATTTTGTCTGTGA  
GCTGTACTACCCAATGCAGTAGTTCGTAGTCAGTGTGGCTCCTGAGCCCT[  
C/T]GAAGTGTAGCTCCTCTGAAGTGAAGACGTGCTGTAAATGTAAATTGCA  
CACCGGAGTTTGAAGAGTTAATACAAAGAAAAAGGAATGCAAAACATCT  
CATTAATAATGCTTTACACTGATTACATATTGAAATGGTAATCTTGTAGAT  
ATAGTGCCTTAAATAAAATATACTGTTAGGCTTAAATTCACGTCTTTATA  
SG13S407

TCAGCCAATCAACAAGAGGGCAAAAGAACAACATTTGATGTGTA  
ATTACTTAATTTAGTGCATATGCATTTGGGTCCTCAATGTCAGCACTATGG  
CAACCAGAACATGGCCACAATACTGTCTGGAAATGTCTATTCTTACCTG  
GACCCAGCAGGCCATGCCCCACTGATTATATAATCTCCCTCTCTCCTTGTT  
A[C/T]GGTCTGAATGCTTGCATCCCTCAAAAATTCATGTGTTGAAATCCTA  
ACCCCCAAGGTGATGATATTAGGAGGTCTGGCCTTTTGAGAGGTAATTAGG  
TCATGAAGACAGCATCCTCATGAATGGGATTAGTGTCTTATAAAATAGG  
CCCAAGGGAGCTCATTCACTTTGTCCACCATGTGAGAACACAGCGAGAGG  
G

SG13S408

CCTTGTTACGGTCTGAATGCTTGCATCCCTCAAAAATTCATGTGTTG  
AAATCCTAACCCCCAAGGTGATGATATTAGGAGGTCTGGCCTTTTGAGAGG  
TAATTAGGTCATGAAGACAGCATCCTCATGAATGGGATTAGTGTCTTATA  
AAATAGGCCCAAGGGAGCTCATTCACTTTGTCCACCATGTGAGAACACAG  
[C/T]GAGAGGGCACCATTTATGCACCAGGAAATGGGCCTTTTCCAGACAAT  
CTGTCCGTGCCTGGATCTTGGACTTCACAGCCTCTAGAACTGTGAGAAAT  
AATTTGTTTTTTTATAAGCCACCAAATCTATGGTTTTTTTTTATAGAAACCGTA  
ATGGACTAAAACACTCCCTAATTATATTTAACTTATCAGTGCCTG  
SG13S7

CTAACCCCCAAGGTGATGATATTAGGAGGTCTGGCCTTTTGAGAGGT  
AATTAGGTCATGAAGACAGCATCCTCATGAATGGGATTAGTGTCTTATA  
AAATAGGCCCAAGGGAGCTCATTCACTTTGTCCACCATGTGAGAACACAG  
CGAGAGGGCACCATTTATGCACCAGGAAATGGGCCTTTTCCAGACAATCT  
GT[C/T]GGTGCCTGGATCTTGGACTTCACAGCCTCTAGAACTGTGAGAAAT  
TAATTTGTTTTTTTATAAGCCACCAAATCTATGGTTTTTTTTTATAGAAACCGT  
AATGGACTAAAACACTCCCTAATTATATTTAACTTATCAGTGCCTG  
AGTGACATATTAAGAAGATGCTGGCCAACGTAATTGACACCATAAGGCT  
SG13S37

TCATCTCATTTTAACTTTTGTCTTCAAAGCCTCTCTTTTCATGACTTC  
CCCGCCTTCATTTTCCCATATGGTGGGGTTATTATTAAGACATTAAATGA  
GAGTGGACAGGTAGGCAAAGGAGGTGGGTTGCAGGGGAGTTGAGGGTTG  
CCTGTGTACTTTTCTAGACTGTTCCACTTCACATCAGTGAAATATTCCCA[A  
/G]TTGATACTATCATGAAACAAAGCAAATGAAATGCTGAGCACGGAGCTT  
CGTCTTGATGAAATGCTGAAAGAAAAGAAAGGAAAAATAAAGTAGCCAT

FIG. 8.38

TATTTTGGCCCTTCCTCCCACCCCATGTTTACTACTCTTATTTCTCTTTTGT  
ATTGTTGTGTTGGAAGCACAGCATCAGAAAACTCCCAGTTTGTGAGA  
SG13S409

ACAGGTAGGCAAAGGAGGTGGGTTGCAGGGGAGTTGAGGGTTGCC  
TGTGTACTTTCTAGACTGTTCCACTTCACATCAGTGAAATATTCCCAATT  
GATACTATCATGAAACAAAGCAAATGAAATGCTGAGCACGGAGCTTCGTC  
TTGATGAAATGCTGAAAGAAAAGAAAGGAAAAATAAAGTAGCCATTATTT  
TT[A/G]CCCTTCCTCCCACCCCATGTTTACTACTCTTATTTCTCTTTTGTAT  
TGTTGTGTTGGAAGCACAGCATCAGAAAACTCCCAGTTTGTGAGAGATAA  
CTCAGTGTTTAGTTCACTTAAACCTGAGAAAGGAGAAGAGGATGCCACCG  
TGAGGTCCAGGACGTAAAGAGGAAAAAAACAGACAAAAAAATCCATATG  
A

SG13S8

CAGGTAGGCAAAGGAGGTGGGTTGCAGGGGAGTTGAGGGTTGCCT  
GTGTACTTTCTAGACTGTTCCACTTCACATCAGTGAAATATTCCCAATTG  
ATACTATCATGAAACAAAGCAAATGAAATGCTGAGCACGGAGCTTCGTCT  
TGATGAAATGCTGAAAGAAAAGAAAGGAAAAATAAAGTAGCCATTATTT  
TG[A/C]CCTTCCTCCCACCCCATGTTTACTACTCTTATTTCTCTTTTGTATT  
GTTGTGTTGGAAGCACAGCATCAGAAAACTCCCAGTTTGTGAGAGATAAC  
TCAGTGTTTAGTTCACTTAAACCTGAGAAAGGAGAAGAGGATGCCACCGT  
GAGGTCCAGGACGTAAAGAGGAAAAAAACAGACAAAAAAATCCATATGA  
A

SG13S410

TTCGTCTTGATGAAATGCTGAAAGAAAAGAAAGGAAAAATAAAGT  
AGCCATTATTTTGGCCCTTCCTCCCACCCCATGTTTACTACTCTTATTTCT  
CTTTTGTATTGTTGTGTTGGAAGCACAGCATCAGAAAACTCCCAGTTTGT  
AGAGATAACTCAGTGTTTAGTTCACTTAAACCTGAGAAAGGAGAAGAGGA  
[C/T]GCCACCGTGAGGTCCAGGACGTAAAGAGGAAAAAAACAGACAAAA  
AAATCCATATGAAATGAAAATGTGAAAGAGGCGCTTTCGAGCAGATGAGT  
GTTGTAGATTACAGTGTTGAGAGCTGTTTGTGTCCAGAGCTGCTTGCTGCA  
CCTGGCGGGATAAACACTGGTCTAACAGAGGATCCTTGTTTCAAGGAGGC  
T

SG13S411

AAGAAAAGAAAGGAAAAATAAAGTAGCCATTATTTTGGCCCTTCCT  
CCCACCCCATGTTTACTACTCTTATTTCTCTTTTGTATTGTTGTGTTGGA  
GCACAGCATCAGAAAACTCCCAGTTTGTGAGAGATAACTCAGTGTTTAGT  
TCACTTAAACCTGAGAAAGGAGAAGAGGATGCCACCGTGAGGTCCAGGA  
C[A/G]TAAAGAGGAAAAAAACAGACAAAAAAATCCATATGAAATGAAAA  
TGTGAAAGAGGCGCTTTCGAGCAGATGAGTGTTGTAGATTACAGTGTTGA  
GAGCTGTTTGTGTCCAGAGCTGCTTGCTGCACCTGGCGGGATAAACACTG  
GTCTAACAGAGGATCCTTGTTTCAAGGAGGCTGCCTTTTATTTGGGGGGAC  
AA

SG13S9

ATTATTTTGGCCCTTCCTCCCACCCCATGTTTACTACTCTTATTTCT  
CTTTTGTATTGTTGTGTTGGAAGCACAGCATCAGAAAACTCCCAGTTTGT  
AGAGATAACTCAGTGTTTAGTTCACTTAAACCTGAGAAAGGAGAAGAGGA  
TGCCACCGTGAGGTCCAGGACGTAAAGAGGAAAAAAACAGACAAAAAA  
[C/T]CCATATGAAATGAAAATGTGAAAGAGGCGCTTTCGAGCAGATGAGT  
GTTGTAGATTACAGTGTTGAGAGCTGTTTGTGTCCAGAGCTGCTTGCTGCA

FIG. 8.39

CCTGGCGGGATAAAACACTGGTCTAACAGAGGATCCTTGTTTCAAGGAGGC  
TGCCTTTTATTTGGGGGGACAAAATTGTTCTTGAAAGCTGCTCAGTGGTT  
SG13S412

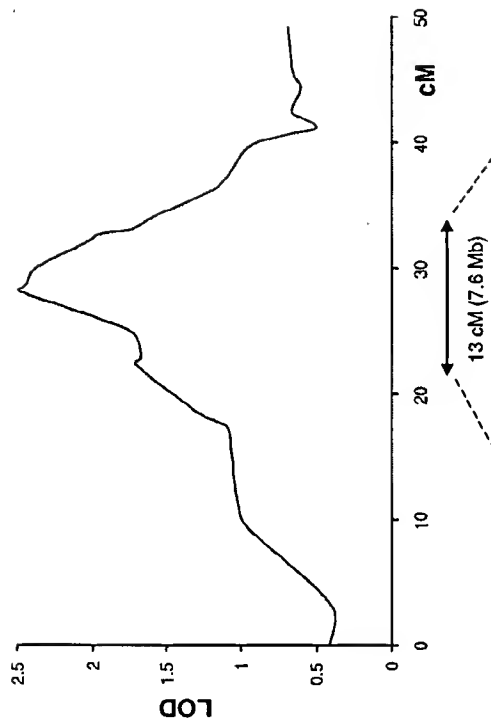
TTTGTATTGTTGTGTTGGAAGCACAGCATCAGAAAAACTCCCAGTT  
TTGAGAGATAACTCAGTGTTTAGTTCACTTAAACCTGAGAAAGGAGAAGA  
GGATGCCACCGTGAGGTCCAGGACGTAAAGAGGAAAAAACAGACAAAA  
AAATCCATATGAAATGAAAATGTGAAAGAGGCGCTTTCGAGCAGATGAGT  
GTT[A/G]TAGATTACAGTGTTGAGAGCTGTTTGTGTCCAGAGCTGCTTGCT  
GCACCTGGCGGGATAAAACACTGGTCTAACAGAGGATCCTTGTTTCAAGGA  
GGCTGCCTTTTATTTGGGGGGACAAAATTGTTCTTGAAAGCTGCTCAGTGG  
TTCAAGCTACAGCATGGTGGACTAGCAGAATGGACTCCAGGGCCTCCGAG  
GA

SG13S413

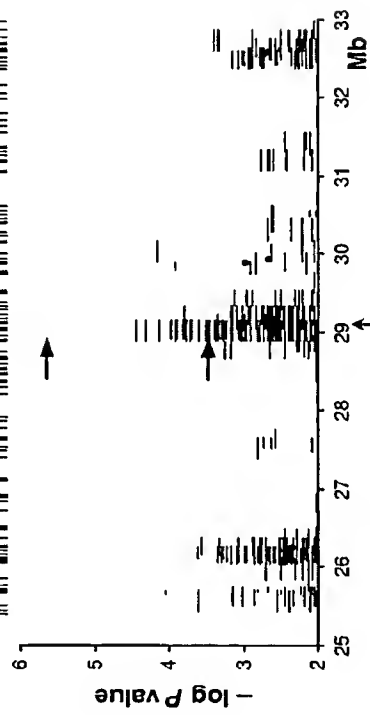
TTTTGAGAGATAACTCAGTGTTTAGTTCACTTAAACCTGAGAAAGG  
AGAAGAGGATGCCACCGTGAGGTCCAGGACGTAAAGAGGAAAAAACAG  
ACAAAAAATCCATATGAAATGAAAATGTGAAAGAGGCGCTTTCGAGCA  
GATGAGTGTTGTAGATTACAGTGTTGAGAGCTGTTTGTGTCCAGAGCTGCT  
TGC[C/T]GCACCTGGCGGGATAAAACACTGGTCTAACAGAGGATCCTTGTTT  
CAAGGAGGCTGCCTTTTATTTGGGGGGACAAAATTGTTCTTGAAAGCTGCT  
CAGTGGTTCAAGCTACAGCATGGTGGACTAGCAGAATGGACTCCAGGGCC  
TCCGAGGAGACAGTGACTGCTGCCAGAAATAGTCAAGGATAGAAAGGAA  
GGA

FIG. 8.40

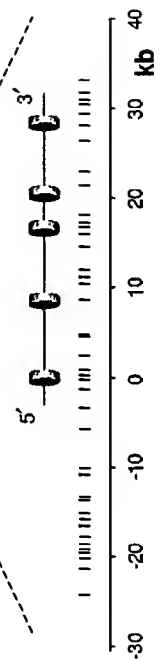
FIG. 9 9.1



9.2 b



9.3 c



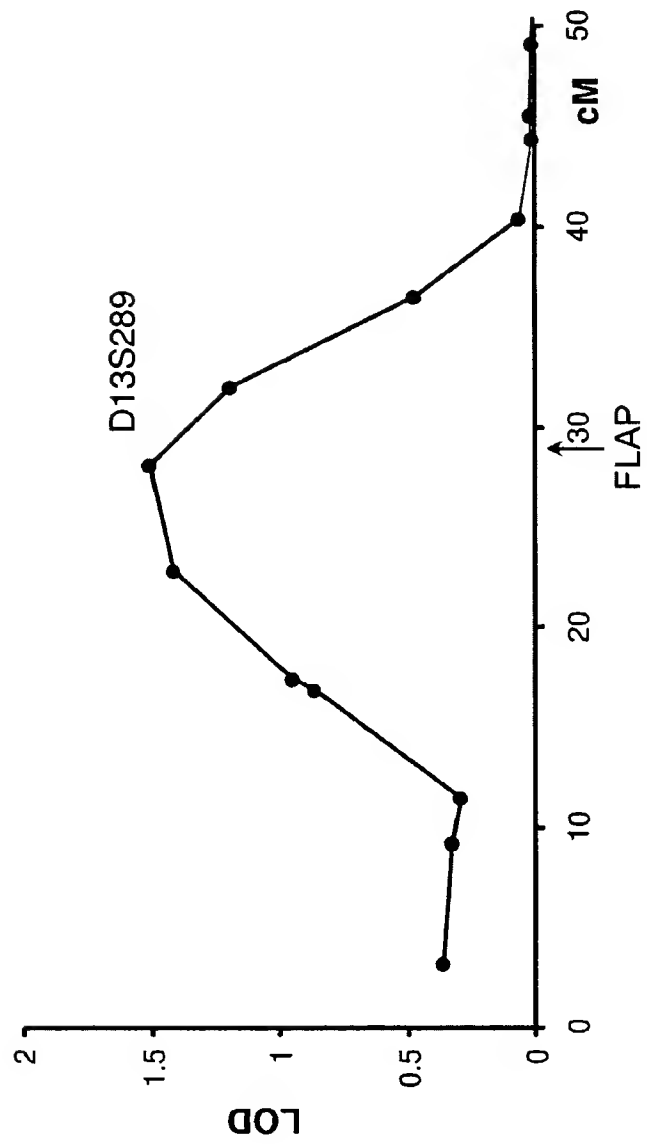


FIG. 10



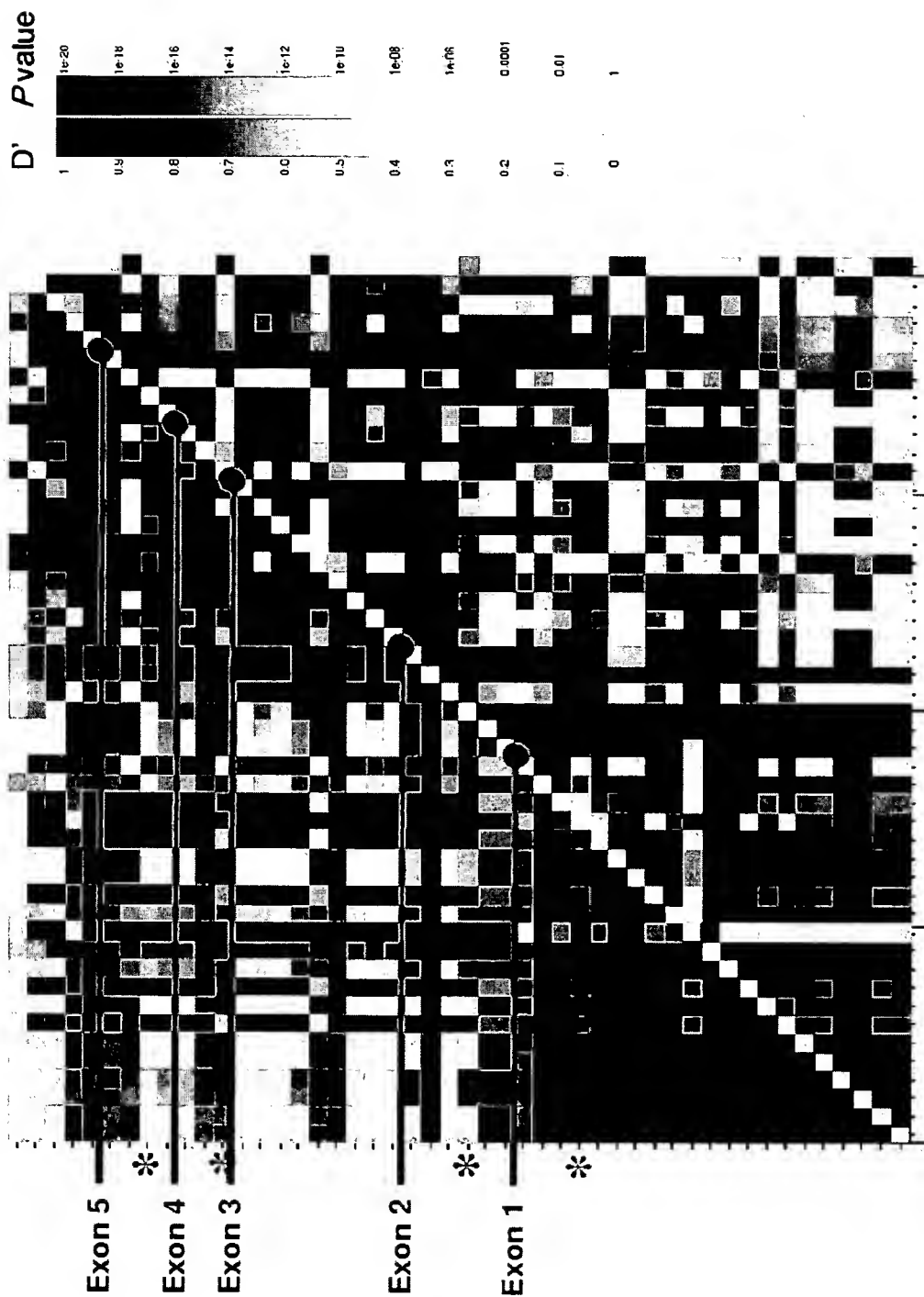


FIG. 11